Mechanistic studies in azo - dye formation

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Mechanistic Studies in Azo - Dye Formation

by

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ABSTRACT

Diazotisation and azo-coupling reactions have been studied and the results are reported.

A kinetic study of the acid catalysed diazotisation of various aniline derivatives has been made. The substrates considered were 2,4-dinitroaniline, 4-nitroaniline, sulphanilamide (aniline-4-sulphonamide) and sulphanilic acid (aniline-4-sulphonic acid). A new pK_a value of 1.4 is reported for sulphanilamide. A study of the diazotisation of sulphanilic acid and sulphanilamide in the presence of Cl^-, Br^-, SCN^-, and $SC(NH_2)_2$ shows that the general catalytic trend $Cl^- < Br^- < SCN^- < SC(NH_2)_2$ is followed, whereas for the corresponding nitrosating agents the general reactivity trend $NOCl > NOBr > NOSCN > NOSC(NH_2)_2^+$ is followed. No catalysis was observed in the case of 2,4-dinitroaniline and this has been interpreted in terms of a rapid reversible nitrosation in which the rate of the denitrosation step is greater than the rate of decomposition of the intermediate nitrosammonium ion. The bimolecular rate constants obtained for sulphanilic acid and sulphanilamide approach the diffusion controlled limit for this process in the case of NOCl and NOBr.
Also reported is a study of the diazotisation of two heteroaromatic amines: 2-amino-5-nitrothiazole and 3-amino-1,2,4-triazole. Catalysis by acid and the nucleophiles Cl^- and SCN^- has been observed. The catalytic and reactivity trends described above have been noted for reaction of these heteroaromatics. The pK_a value for 2-amino-5-nitrothiazole has been determined and agrees well with the literature values.

In addition to the above studies of diazotisation mechanisms, results are reported of a study of the leaving abilities of various electrofugal leaving groups X during ipso-coupling of 4-nitroaniline with 4-X-N,N-dimethylanilines. The sequence of leaving abilities has been determined by product yield studies. Rate constants for attack of ArN_2^+ have also been determined. It is suggested that a substrate molecule ($X-Ar-NMe_2$) acts as a base in removing the group X from the Wheland intermediate.

MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1982 and September 1985 and has not been submitted for any other degree. It is the original work of the author except where acknowledged by reference.

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If we cannot know something without knowing everything, then it is obvious that we can never know something

— Bertrand Russell

To my Mother and Sue

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CHAPTER 1

GENERAL INTRODUCTION to MECHANISMS of DIAZOTISATION

1.1 General Introduction.

In 1858 Peter Greiss[1] discovered the diazotisation reaction and shortly thereafter synthesised the first azo-dye. By the end of the nineteenth century the dyestuffs industry had emerged as one of the most lucrative of all and interest in the reactions leading to the formation of azo-dyes - now the largest and most versatile class of dyes - was aroused. Since then research has shown the diazotisation reaction to be one of the most interesting and yet one of the most complex problems of organic chemistry and many reviews and monographs on the subject have been published[2-5].

Researches into the mechanism of diazotisation are based on the supposition by Bamberger[6] that the reaction involves an initial N-nitrosation of the amine. This is supported by the fact that the rate of nitrosation of N-methylaniline in acid solutions of concentrations up to 6.5M parallels exactly the rate of diazotisation of aniline[7]. The similarity between the two reactions provides the strongest evidence that the rate determining step in diazotisation is also an N-nitrosation[8].

The diazotisation reaction as a whole involves several steps as shown in scheme 1.1.

$$ArNH_2 \xrightarrow[\text{slow}]{NOY} ArNH_2^+NO \xrightarrow{-H^+} ArNHNO \longrightarrow ArN{=}NOH \xrightarrow{-OH^-} ArN_2^+$$

SCHEME 1.1

Generally the free base form of the amine is the reactive species here. In the case of a secondary amine the reaction stops after loss

of a proton because a prototropic change to the diazohydroxide is not possible, and with primary aliphatic amines the reaction continues with the formation of a variety of deamination products[2].

The nitrosating agent, NOY, is a species derived from nitrous acid and can be regarded simply as a carrier of the nitrosonium ion, NO^+. Several nitrosating agents can be formed, their exact nature depending upon the acidity of the medium and the presence of such nucleophiles as halide ion, thiocyanate, and thiourea. these nucleophiles act as catalysts by reacting with the nitrous acidium ion, $H_2NO_2^+$ formed by protonation of nitrous acid, and forming covalent nitrosyl species (NOY) which react with the amine as shown in scheme 1.1. Nitrous acid itself is thought to be too unreactive to nitrosate amines directly[9].

The nitrosating agents under consideration in the present work are shown in table 1.1. This list is not comprehensive but these are considered the most effective nitrosating agents. The different mechanisms of diazotisation are described in the following sections.

$$H_2NO_2^+ + Y^- \rightleftharpoons NOY + H_2O$$

Y^-	NOY	
NO_2^-	N_2O_3	Nitrous anhydride
-	$H_2NO_2^+$	Nitrous acidium ion
-	NO^+	Nitrosonium ion
Hal^-	NOHal	Nitrosyl halide
SCN^-	NOSCN	Nitrosyl thiocyanate
$SC(NH_2)_2$	$NOSC(NH_2)_2^+$	S-Nitrosothiouronium ion

TABLE 1.1

1.2 The Nitrous Anhydride Mechanism.

Early investigations[10] into the mechanism of diazotisation of aniline and amines of similar basicity at low acidity (ca. 10^{-3}M HCl) showed the reaction to be second order overall and since only two reactants were involved the order with respect to each was assumed to be unity. Equation 1.1 was proposed by Hantzsch and Schümann[10]:

$$\text{RATE} = k[ArNH_3^+][HNO_2] \qquad (1.1)$$

Although no direct evidence was obtained to show that the protonated amine was the reactive species, it was reasoned that since all of the amines used in the study reacted at the same rate, the conjugate acid of each amine must be involved as the amines would be almost completely protonated. This was supported by other workers for diazotisation[11] and deamination[12].

In 1928 Taylor[13] showed that the deamination of methylamine was third order overall as expressed by equation 1.2.

$$\text{RATE} = k[RNH_2][HNO_2]^2 \qquad (1.2)$$

Taylor obtained the same result for reaction of ammonia with nitrous acid and the following year published the results of a study which suggested for the first time that the kinetic form of equation 1.2 could be associated with a rate determining nitrosation[14]. Schmid[15] later obtained an equivalent kinetic form for diazotisation of aniline in sulphuric acid (ca. 0.2M).

For some time there was considerable disagreement over which of these two equations should be accepted, but the situation was finally resolved by Hammett[16] who suggested that nitrosation by nitrous anhydride (scheme 1.2) would result in third order kinetics as in equation 1.2.

$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O$$

$$N_2O_3 + ArNH_2 \longrightarrow ArNH_2^+NO + NO_2^-$$

$$ArNH_2^+NO \downarrow \rightarrow ArN_2^+$$

SCHEME 1.2

Although this suggestion was not immediately accepted it has been shown to be correct and leads to the reconciliation of equations 1.1 and 1.2. At low acidities (ca. 10^{-3}M $HClO_4$) and with reactant concentrations of the order 10^{-3}M the concentration of free amine is sufficient to react with the nitrous anhydride before a significant proportion has undergone hydrolysis to nitrous acid[17]. This means that the nitrous anhydride reacts as quickly as it is formed and the rate determining stage is thus formation of N_2O_3 rather than its attack on the amine. Therefore, under these conditions, the overall reaction rate depends upon a slow inorganic reaction and rate equation 1.3 was obtained. Since the acidity used to establish 1.3 was the same as that used by Hantzsch and Schümann[10] there is little

doubt that they were essentially observing diazotisation according

$$\text{RATE} = k[HNO_2]^2 \qquad (1.3)$$

to 1.3 but were unable to distinguish between 1.1 and 1.3 because they were using equal reactant concentrations. The fact that the reaction rates were the same for several amines can also be explained by reference to equation 1.3 which is, of course, independent of amine nature and concentration.

Bunton, Llewellyn, and Stedman[18] studied the incorporation of ^{18}O-labelled water into nitrous acid (the pre-equilibrium step in scheme 1.2) and found that the rate of this exchange is second order in $[HNO_2]$ and is much the same as diazotisation in weakly acidic media. This provides further support for the validity of equation 1.3. Thus the diazotisation of very basic amines follows equation 1.3 at low acidities and equation 1.2 under moderately acidic conditions (ca. 0.1M) after passing through a region of intermediate order[17a]. This change occurs because an increase in the acidity of the medium results in a decrease in the concentration of reactive free amine which is accompanied by a change in the rate determining step from formation of N_2O_3 to its attack on the amine. Weakly basic amines react slowly with N_2O_3 and so diazotisation follows equation 1.2 even at very low acidities[19]. For aniline ($pK_a = 4.6$) transition to third order kinetics is complete at about 0.1M H^+ [17a].

In order to determine the bimolecular rate constant for reaction of a substrate with a nitroating agent (i.e. for the rate determining

step in scheme 1.2) the equilibrium constant for formation of the nitrosating agent must be known. The equilibrium constant for formation of nitrous anhydride was originally determined[20] independently by two groups as

$$[N_2O_3]/[HNO_2]^2 = 0.2\ dm^3 mol^{-1}$$

and this value was generally accepted until recently when it was redetermined[21] as $3.03 \times 10^{-3}\ dm^3 mol^{-1}$. This new value, if accepted, means that the previously determined rate constants for the nitrosation step in scheme 1.2 are necessarily about 10^2 times greater than was previously thought. For example, the rate constant for reaction of aniline with N_2O_3, using the old K value, was about $10^7\ mol^{-1}dm^3s^{-1}$ at 25°C. This converts to a value of about $10^9\ mol^{-1}dm^3s^{-1}$ using the new K value and this is now quite close to the diffusion controlled limit for a bimolecular encounter[22], indicating that N_2O_3 is not such a weak electrophile as had previously been thought and may indeed be as reactive as the nitrosyl halides[23] (see later).

The uncertainty of the equilibrium constant value for formation of nitrous anhydride highlights the problem of calculating rate constants for processes involving pre-equilibria. If the rate constants are to be meaningful then the equilibrium constants for formation of reactive species' must be reliable and by the same token amine pK_a values must be accurately determined. Also the early controversy surrounding the acceptability of equations 1.1 and 1.2 shows that a rule of chemical kinetics should always be adhered to:

the order with respect to each reactant must be determined.

Although this mechanism was not studied in the present work it is important to bear in mind the conditions under which it becomes significant so that it can be avoided in the study of the mechanisms described in the following sections.

1.3 Acid Catalysed Diazotisation.

Since increasing the acidity of the medium results in an increase in the concentration of the protonated amine, it seems reasonable to assume that the reaction rate should decrease with increasing acidity as the concentration of reactive free amine diminishes and this is true initially for the more basic amines, such as aniline, which undergo diazotisation by N_2O_3[19]. However, Hughes, Ingold, and Ridd[24] found that the diazotisation of 4-chloroaniline in dilute perchloric acid followed equation 1.4, and the same behaviour was observed by Larkworthy[19] for diazotisation of the nitroanilines.

$$\text{RATE} = k[ArNH_2][HNO_2][H^+] \qquad (1.4)$$

For the more basic amines the acid - rate profile passes through a minimum as $[H^+]$ increases, after which equation 1.4 applies. This indicates that the nature of the nitrosating agent differs from that at low acidities since only one mole of nitrous acid appears in the rate equation and the reaction rate is now proportional to the acidity. This equation is consistent with a mechanism involving rate determining attack by the nitrous acidium ion[25], $H_2NO_2^+$,

present in very low equilibrium concentrations, or its dehydrated form, the nitrosonium ion, NO^+ (scheme 1.3).

$$HNO_2 + H^+ \rightleftharpoons H_2NO_2^+$$

$$H_2NO_2^+ \rightleftharpoons NO^+ + H_2O$$

SCHEME 1.3

There is no hard evidence for either of these species at low to moderate acidities - in fact there is no spectral evidence at all for the existence of $H_2NO_2^+$, although it may be involved and is generally accepted to be so[23]. The Nitrosonium ion has been observed in strongly acidic solutions and the equilibrium constant for its formation has been determined[26] spectrophotometrically as 3.03×10^{-7} dm^3mol^{-1}. Thus at high acidities there is no reason to doubt that the nitrosonium ion is the effective electrophile. The problem arises at lower acidities from which most of the kinetic evidence for equation 1.4 has been obtained.

Benton and Moore[27] studied the nitrosation of hydrogen peroxide at low acidities under first-order conditions ($[H_2O_2] \gg [HNO_2]$) and found that the observed first-order rate constant (measured as a function of $[H_2O_2]$) reached a limiting value at about 1M H_2O_2. They argued that since the reaction had become zero-order in hydrogen peroxide, the rate determining step had changed to formation of the nitrosating agent and as formation of $H_2NO_2^+$ involves a very fast

proton transfer they were essentially observing rate determining formation of NO^+. However, it has been suggested[22] that this change to zero-order kinetics arises from a medium effect and recently[28] supporting evidence for this suggestion has been published. Yet more evidence against the involvement of NO^+ at low acidities arises from the rate of ^{18}O exchange between nitrous acid and water[29] and from theoretical calculations on the structure and reactivity of nitrosating agents[30]. Perchloric acid was used as a source of H^+ in these and subsequent studies. The possibility of nitrosation by nitrosyl perchlorate ($ONClO_4$), though, can be ruled out as perchlorate does not form covalent nitrosyl compounds[26,31].

Thus, nitrosation under moderately acidic conditions occurs as in scheme 1.4.

$$HNO_2 + H^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} H_2NO_2^+$$

$$H_2NO_2^+ + ArNH_2 \xrightarrow{\text{slow}} ArNH_2^+NO + H_2O$$

$$ArNH_2^+NO \xrightarrow{\text{several steps}} ArN_2^+$$

SCHEME 1.4

Larkworthy[19] has measured rate constants (equation 1.4) for reaction of weakly basic amines in acid solutions up to 0.5M and found that the values did not vary appreciably with amine pK_a. This indicates that $H_2NO_2^+$ does not discriminate in its reactions whereas the less

reactive N_2O_3 showed considerable variation (by a factor of ca. 50) and in fact failed to react with weak bases such as 4-nitroaniline. Since third-order rate constants (equation 1.4) approach a limiting value for many substrates, it has been suggested[22] that this represents the diffusion controlled limit for acid catalysed reactions. Bimolecular rate constants for encounter between aniline derivatives and nitrosyl halides (section 1.5) have been shown[32] to approach a diffusion controlled limit and since $H_2NO_2^+$ is considered a stronger electrophile than these species it is expected that encounter between aniline derivatives and $H_2NO_2^+$ will also be diffusion controlled. However, bimolecular rate constants for reaction of substrates with $H_2NO_2^+$ cannot be determined as the equilibrium constant for protonation of nitrous acid is not known.

Increasing the acidity further (up to about 3M $HClO_4$) has two effects on the rate profile. Firstly, under these conditions, the reaction is subject to acceleration due to a salt effect[33], which can be countered by the addition of a large excess of a neutral perchlorate salt. Secondly, for the less basic amines, the increase in acidity is offset by a decrease in the concentration of free base resulting in an almost zero-order dependence on the acidity. Due to the relatively high acid concentration here it is more appropriate to use an acidity function in place of $[H^+]$ in the rate equation[34]:

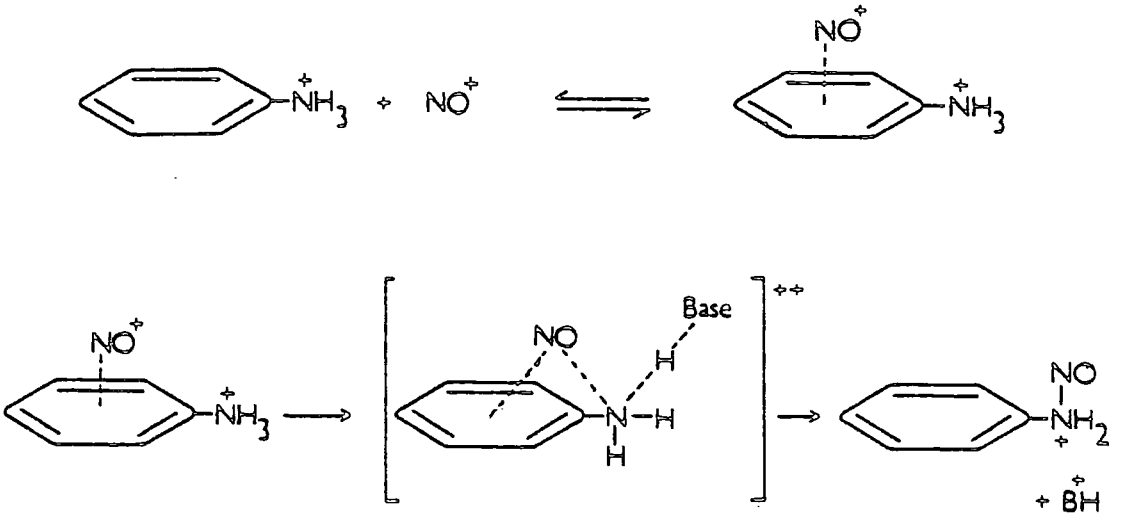
$$\text{RATE} = k[ArNH_2][HNO_2]h_o \qquad (1.5)$$

The mechanism here is the same as before - i.e. rate determining attack of $H_2NO_2^+$ on the free base form of the amine.

For aromatic amines more basic than the nitroanilines the incursion of a second term into equation 1.5 has been observed under these conditions:

$$\text{RATE} = k[ArNH_2][HNO_2]h_0 + k'[ArNH_3^+][HNO_2]h_0 \qquad (1.6)$$

This has been explained[35,36] in terms of an attack of the nitrosating agent on the aromatic ring of the protonated amine initially, followed by a rate determining rearrangement to the amino nitrogen which is concurrent with proton loss, usually to the solvent (scheme 1.5).



SCHEME 1.5

This mechanism is particularly important for strongly basic amines which are almost completely protonated under these conditions. An analogous reaction was studied by Thompson and Williams[37], who found

that anilinium ion was diazotised by N-nitrosodiphenylamine with a similar rate law, whereas aliphatic amines did not react.

1.4 Diazotisation At High Acidities.

A further increase in the acidity (>6M $HClO_4$) results in a decrease in the reaction rate according to equation 1.7

$$RATE = k[ArNH_3^+][HNO_2]h_o^{-2} \qquad (1.7)$$

This behaviour has been observed for aniline, 4-nitroaniline, and 4-toluidine[34]. Raman studies[38] have shown that under these conditions of low water activity the nitrosating agent is NO^+ and the mechanism shown in scheme 1.6 has been proposed to explain the large isotope effect[34] ($k_H/k_D = 10$).

$$NO^+ + ArNH_3^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} ArNH_2^+NO + H^+$$

$$ArNH_2^+NO + Base \xrightarrow{\text{slow}} ArNHNO + BH^+$$

$$ArNHNO \xrightarrow{\text{fast}} ArN_2^+$$

SCHEME 1.6

The reduction in the rate is thought to be due to a change in the rate determining step from the initial nitrosation to deprotonation of the nitrosoanilinium ion. The reduction in rate is brought about

by two factors. Firstly, N-nitrosation can become reversible at high acidities as displacement of NO^+ by a proton is favourable and rapid, and secondly proton transfer to a highly acidic medium is unfavourable.

1.5 Halide Ion Catalysis.

In 1937 Schmid[39] published the results of a study involving diazotisation in the presence of halide ions, although catalysis of the reaction by halide ions in the form of hydrohalic acids had been reported earlier[40]. Schmid proposed equation 1.8 to account for this behaviour.

$$\text{RATE} = k[\text{Amine}][HNO_2][H^+][X^-] \qquad (1.8)$$

This refers to the nucleophile catalysed reaction, where $X^- = Cl^-$, Br^-, or I^-, but the overall rate equation for the reaction will also include a term in the non-nucleophile catalysed reaction, depending upon the acidity, as described in the previous sections. Diazotisation in perchloric or sulphuric acid solutions containing added halide also follows 1.8.

Hammett[16] suggested that the above equation is consistent with rate determining reaction via a nitrosating agent NOX formed by attack of halide on the nitrous acidium ion, as shown in scheme 1.7. It was reasoned[25] that since catalysis by X^- was observed in conditions under which formation of N_2O_3 was measurably slow, the nitrosating agent was not formed by interaction of the halide ion with N_2O_3. The fact that the formation of NOX requires protonation of

nitrous acid suggests that other nitrosating agents are formed in the same manner. Thus, for example, nitrous anhydride is formed from $H_2NO_2^+$ and NO_2^- rather than two molecules of nitrous acid[3].

$$H_2NO_2^+ + X^- \underset{k_{NOX}}{\overset{fast}{\rightleftharpoons}} NOX + H_2O$$

$$ArNH_2 + NOX \xrightarrow[k_2]{slow} ArNH_2^+NO \xrightarrow{fast} ArN_2^+$$

SCHEME 1.7

Support for Hammett's suggestion was provided by Hughes and Ridd[25] who carried out their reactions using a suitable excess of amine so that the nitrosating agent reacted as soon as it was formed. This resulted in rate determining formation of NOX according to 1.9 a situation analogous to that in the nitrous anhydride mechanism described earlier.

$$RATE = k[HNO_2][H^+][X^-] \qquad (1.9)$$

This corresponds to attack of X^- on $H_2NO_2^+$, as the reaction is first-order in nitrous acid[17b]. Although Hughes and Ridd were able to achieve this condition in reactions catalysed by bromide and iodide, it was not possible to achieve rate determining formation of nitrosyl

chloride. The electronegativity differences between the halides suggest that NOCl should be polarised to a greater extent than both NOBr and NOI thus making it a much more reactive electrophile, and rate determining formation of NOCl under the above conditions might reasonably be expected. However, it is the effect of the electronegativity of the chlorine atom on the equilibrium concentration of NOCl that is the important factor. The concentration of NOCl is never large enough for it to react faster than it is formed. This reasoning can be extended to explain the fact that catalysis by fluoride is not observed[25]. Although it was not possible to make formation of NOCl rate controlling for aniline derivatives, Stedman was able to achieve this condition for the nitrosation of azide ion in an azide / hydrazoic acid buffer solution[41].

Equilibrium constants (K_{NOX}) for formation of NOCl and NOBr at 25°C have been determined as $1x10^{-3}$ dm^6mol^{-2} and $5x10^{-2}$ dm^6mol^{-2} respectively[42,43]. Iodine formation prevents the determination of K_{NOI}[44]. The method used to determine K_{NOCl} has been criticised[45] and in view of the uncertainty over the equilibrium constant value for formation of N_2O_3, redetermination of these K_{NOX} values may be timely, although they have been widely used and lead to sensible bimolecular rate constants for reaction of NOX with, for example, aniline derivatives[32].

Using these equilibrium constant values, Schmid calculated the bimolecular rate constants k_2 (scheme 1.7) defined by 1.10 for nitrosation via NOCl[42,46,47] and NOBr[43,46]. Rate constant values for reaction of NOCl with a number of aniline derivatives were all

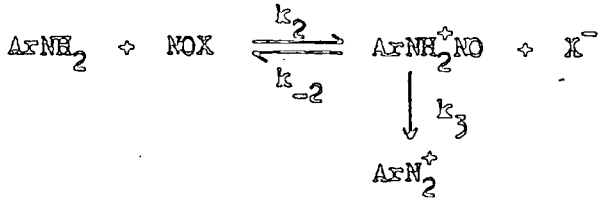
in the range $1-3\times10^9$ $dm^3mol^{-1}s^{-1}$ at 25°C and Schmid originally

$$RATE = k_2[ArNH_2][NOX] \qquad (1.10)$$

attempted to correlate these with amine basicities. Obviously the dependence is very slight since the basicities differed by a factor of as much as 250. Schmid calculated these rate constants on the basis of a small number of observations and later conflicting results were obtained by Williams[48], who used an indirect method to determine the reactivities of NOX species towards aniline derivatives. The results showed that, for NOCl, a certain dgree of discrimination occurred. Crampton, et al[32], studied the diazotisation of several aniline derivatives, common to both the studies of Schmid and Williams, and found that for amines with low pK_a values, e.g. 4-nitroaniline ($pK_a = 1.0$), NOCl was considerably more reactive than NOBr, as expected, whereas the reactivity difference was only slight for amines of $pK_a > 4$. Plots of $\log k_2$ (equation 1.10) versus pK_a curved off to a limiting value of ca. 7×10^9 $dm^3mol^{-1}s^{-1}$. It is now generally accepted that rate constant values of this order represent the diffusion controlled limit for a bimolecular encounter[22]. Here a direct comparison can be made between the k_2 values for reaction of the nitrosyl halides and the corrected values of ca. 10^9 $dm^3mol^{-1}s^{-1}$ for N_2O_3.

In certain cases the reversibility of the initial nitrosation may become important[49] (scheme 1.8). This has been noted particularly for the more nucleophilic X^- species at high $[X^-]$ and for those substrates which carry electron withdrawing groups[32]. In fact, for some

such substrates the position of equilibrium lies so far over to the side of the reactants that no halide catalysis is observed at all.



SCHEME 1.8

This is the case with sulphamic acid[50], methylurea[51], and amides in general[52]. In the present work diazotisation of 2,4-dinitroaniline exhibited no catalysis by nucleophilic species and this will be discussed in detail in chapter 3.

1.6 Catalysis By Thiocyanate And Thiourea.

The strong catalytic effect exerted by the halides has led to the search for other, possibly more efficient, nucleophilic species capable of accelerating the rate of diazotisation. This interest arises particularly from the fact that secondary amines present in the body can undergo nitrosation to form highly carcinogenic N-nitrosamines[53], and there is an obvious need to identify potential catalysts for these processes. For example, hydrochloric acid is present in the stomach and sodium nitrite is used as a preservative in cured meats, and together these form the necessary ingredients to effect nitrosation. Thiocyanate, present in saliva, has been shown to be an efficient catalyst and, in fact, is much more effective than either chloride

or bromide[23]. In smokers the concentration of thiocyanate in the saliva is much greater than in non-smokers[54] and this could be one of the causes of smoking-induced cancer[55].

Nitrosyl thiocyanate is stable only in solution and is observable as a blood-red species ($\varepsilon_{max} = 100$)[56]. The structure of the molecule is not known with certainty, although from Hard-and-Soft Acid-Base (HSAB) theory[57] and the results of recent ab-initio molecular orbital calculations[58], it would seem that the NO group is attached to the sulphur atom rather than nitrogen. This is an example of S-nitrosation:

$$H_2NO_2^+ + SCN^- \rightleftharpoons ONSCN + H_2O$$

The equilibrium constant for this reaction has been determined[56] as $K_{NOSCN} = 30\ dm^6 mol^{-2}$ at 25°C. Thiocyanate catalysis occurs in the same manner as halide catalysis ($X^- = SCN^-$ in scheme 1.7) and the kinetics are identical. Bimolecular rate constants have been obtained for reaction of NOSCN with inorganic substrates[59], as well as with aliphatic amines[60] and derivatives of aniline[18,28] and these were generally about 100 times less than for nitrosyl bromide. Nitrosyl iodide may be about as reactive as NOSCN, but quantitative information is lacking since K_{NOI} is not known.

Catalysis by thiourea has also been observed and in this case reaction with $H_2NO_2^+$ leads to formation of an unstable yellow species which has been observed spectrophotometrically in solution:

$$H_2NO_2^{\oplus} + SC(NH_2)_2 \rightleftharpoons ONS\overset{\oplus}{C}(NH_2)_2 + H_2O$$

Again, the kinetics of nitrosation by this species are the same as for the nitrosyl halides and the catalytic effect of thiourea has been studied[28,60]. Equilibrium constants (at 25°C) for the formation of the S-nitrosothiouronium ion and the other nitrosating species mentioned in this section are summarised in table 1.2.

X^-	$K_{NOX}/dm^6 mol^{-2}$	ref.
Cl^-	1.1×10^{-3}	42
Br^-	5.1×10^{-2}	43
SCN^-	30	56
$SC(NH_2)_2$	5000	61

TABLE 1.2

Brönsted plots ($\log k_2$ vs pK_a) for reaction of NOX species with several aniline derivatives were linear for NOSCN and $NO\overset{\oplus}{S}C(NH_2)_2$[28] whereas for the less discriminating NOCl and NOBr the plots levelled off, as mentioned earlier[32].

For a general substrate S the reactivities of these NOX species in the reaction

$$NOX + S \xrightarrow{k} \overset{\oplus}{S}\text{-}NO + X^-$$

always follow the qualitative sequence[23]:

$$NOCl > NOBr > NOSCN > NO\overset{+}{S}C(NH_2)_2$$

whereas the equilibrium constants for formation of these species follow the opposite trend, as shown in table 1.2. An explanation for both of these trends is afforded by HSAB theory[57]. NO^+ is a borderline acid and aniline derivatives (for example) are borderline bases. Therefore, reaction between the two should result in a relatively stable acid-base complex. The bases (X^-) become increasingly soft along the sequence

$$Cl^- < Br^- < SCN^- < SC(NH_2)_2$$

and so less inclined to give up the borderline NO^+ to the amino group (hence the greater reactivity of NOCl) or the solvent (hence the greater K_{NOX} value for the S-nitrosothiouronium ion). The extent of catalysis depends on both the rate constant, k (above), and the equilibrium constant for formation of NOX, but it is the latter that has a greater effect on the overall reaction rate[23]. Thus, thiourea, with $K_{NOX} = 5000\ dm^6 mol^{-2}$, has been found to be one of the best catalysts for nitrosation processes.

1.7 Alternative Reagents And Reactions.

Other nitrosating agents have been identified, for example N_2O_4, $N_2O_2^+$, and $N_2O_3^+$, formed in the presence of NO_3^-, NO, and NO_2

respectively[62]. Catalysis by carboxylate ion has been observed but is thought to be an indirect effect as acetate has been shown to catalyse the formation of N_2O_3[17b,63]. More recently, however, direct nitrosation of N-methylaniline and piperazine by nitrosyl acetate has been reported[64].

Nitrosation reactions are not restricted to nitrogen sites. Many examples of O- and S- nitrosation can be found in the literature, as well as C-nitrosations and the formation of metal nitrosyl complexes. However, these reactions, the details of which may be found in refs. 23 and 65, are outside the scope of the present work.

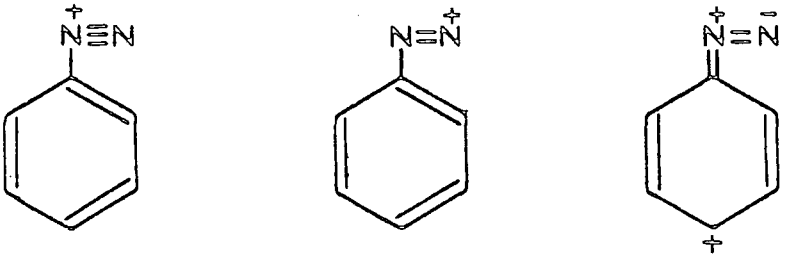
1.8 Structure And Reactivity Of Diazonium Ions.

After his discovery of 1858[1], Peter Greiss gave the name 'Diazo' to his new class of compounds as he believed two hydrogen atoms of the benzene nucleus had been replaced by nitrogen. In later years theories on the structure of these compounds abounded and every combination of benzene with two nitrogen atoms was proposed as the 'correct' structure. It was not until the demonstration[66] in 1878 that penta-substituted anilines underwent diazotisation without loss of a substituent that the idea of the presence of just one C-N bond in the molecule was accepted. These and later theories on the structure of diazo compounds have been reviewed by Saunders[5].

The modern view, supported by experimental evidence, is of an aromatic compound containing a single C-N bond and a triple N-N bond[67]

Aliphatic diazonium ions are, in the vast majority of cases, extremely unstable and may have only a fleeting existence, losing nitrogen to form deamination products[2]. In contrast, aromatic diazonium ions, whilst not indefinitely stable in solution, have much longer lifetimes and can be isolated as salts[68]. Most diazonium salts, though, are very sensitive and many (e.g. nitrates) detonate easily. For this reason diazonium compounds for use in synthetic chemistry are generated in solution and reacted without isolation[69].

The greater stability of the aromatic diazonium ions can be explained in terms of the resonance structures I - III.



I II III

This charge delocalisation, which is of course not possible in aliphatic diazonium ions, increases the stability of the C-N bond and so reduces the leaving ability of nitrogen.

X-Ray studies on several ArN_2^+ compounds have shown the N-N bond distance to lie in the range 0.109 - 0.111 nm, which is virtually the same as that observed in molecular nitrogen[70], indicating that in the electronic ground state resonance form I predominates over II and III[68,71]. Further evidence for this is provided by infra-red studies in which the N-N bond is shown to have a frequency of about

2290 cm^{-1} (ref. 72) which is between the Raman frequency for molecular nitrogen (2330 cm^{-1})[73] and the stretching frequency for the cyano group (2255 cm^{-1} for PhCN)[74]. N-N bond multiplicities have been determined and lie in the range 2.65 - 2.85 [67].

The reactions of aromatic diazonium ions are of two types: those in which nitrogen is lost, and those in which it is retained. Examples of the former - known as dediazoniation - are the Sandmeyer, Scheimann, Meerwein, and Gomberg reactions[75]. By far the most important and widely used example of the second type is the azo-coupling reaction which takes place between a diazonium ion and, usually, an aromatic amine or phenol, and results in the formation of an azo-dye. This is described in detail in chapter 5. Diazonium ions also couple with compounds containing active methylene groups (e.g. the Japp- Klingmann reaction) and with alcohols to form diazo ethers[76]. Many other examples can be found in reference 68, parts 1. and 2.

The following chapters report the results obtained in studies of the diazotisation mechanisms described. Chapter 5 reports a study of azo-coupling.

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CHAPTER 2

ACID CATALYSED DIAZOTISATION of ANILINE DERIVATIVES

2.1 Introduction.

In this chapter are presented the results obtained in studies of the acid catalysed diazotisation of four aniline derivatives. This work was carried out in order to establish the kinetic method to be applied later to the heteroaromatic amines (chapter 4) and also to extend some earlier work in this area[1,2]. The amines under consideration were : Sulphanilic Acid (aniline-4-sulphonic acid), Sulphanilamide (aniline-4-sulphonamide), 4-Nitroaniline, and 2,4-Dinitroaniline.

Normally, reactions would be carried out under first-order conditions with amine concentration in at least 20-fold excess of nitrous acid. However, in the case of the nitroanilines, low amine solubility prevented this and so first-order conditions were achieved with $[HNO_2] \gg [Amine]$. All reactions were carried out at 25°C and perchloric acid was used as a source of H^+ since nitrosyl perchlorate ($ONClO_4$) is completely dissociated in solution[3] and so can be ruled out as a nitrosating agent. Good first-order dependence on $[HNO_2]$ was demonstrated by the linearity of the 'log(a-x)' vs 'time' plots, and complications due to the nitrous anhydride mechanism were not observed. For sulphanilic acid and sulphanilamide first-order dependence on amine concentration was demonstrated. 4-Nitroaniline and 2,4-dinitroaniline have been studied previously[1] (at 0°C) and the order with respect to each substrate was shown to be unity.

Reactions were carried out in either a conventional UV/VISIBLE spectrophotometer or a stopped flow instrument and monitored at constant wavelength by following either the increase in absorbance due to product formation (ArN_2^+) or decrease due to diminishing reactant concentration.

Rate constants quoted in the following sections are averages of 3 to 5 individual kinetic runs, usually reproducible to ±5%. Full details of the methods used and the treatment of errors can be found in chapter six.

2.2 The Kinetic Equation

Hughes, Ingold, and Ridd[4] studied the acid catalysed diazotisation of 4-chloroaniline at 0°C in moderately acidic solutions and obtained equation 1.4, which is reproduced here as 2.1 for convenience.

$$\text{RATE} = k_3[\text{ArNH}_2][\text{HNO}_2][\text{H}^+] \qquad (2.1)$$

As it stands, this equation provides no information about the bimolecular reaction between the nitrosating agent and the amine and is inconvenient as it is written in terms of molecular ('free') concentrations. Consider the rate-determining step:

$$\text{RATE} = k_2[\text{ArNH}_2][\text{H}_2\text{NO}_2^+] \qquad (2.2)$$

We can replace the molecular amine concentration with its stoicheiometric ('total') concentration as follows:

Firstly, we have

$$[\text{ArNH}_2]_T = [\text{ArNH}_2]_F + [\text{ArNH}_3^+]$$

where subscripts refer to total and free concentrations.

Secondly :

$$K_a = \frac{[ArNH_2][H^+]}{[ArNH_3^+]}$$

Combining these two expressions gives

$$[ArNH_2]_F = \frac{K_a[ArNH_2]_T}{[H^+] + K_a}$$

and substitution into 2.2 gives

$$RATE = \frac{k_2K_a[ArNH_2]_T[H_2NO_2^+]}{[H^+] + K_a}$$

Now, the equilibrium constant for the formation of $H_2NO_2^+$ is given by

$$K_N = \frac{[H_2NO_2^+]}{[HNO_2][H^+]}$$

therefore, we can write

$$RATE = \frac{k_2K_NK_a[ArNH_2]_T[HNO_2][H^+]}{[H^+] + K_a} \qquad (2.3)$$

It is evident from this that if 2.1 is expressed in terms of the

stoicheiometric amine concentration we have :

$$k_3 = k_2K_N$$

which is an illustration of how the evaluation of bimolecular rate constants require the accurate knowledge of the equilibrium constant for the formation of the nitrosating agent

Under first-order conditions ($[\text{amine}] \gg [HNO_2]$) we can take this a step further by writing

$$\text{RATE} = k_o[HNO_2]$$

where

$$k_o = \frac{k_3K_a[ArNH_2]_T[H^+]}{[H^+] + K_a} \qquad (2.4)$$

By varying $[H^+]$ a range of values of k_o can be obtained and this is the key to evaluating the rate constant k_3. Clearly there are two possible limiting forms, depending on the acidity and the nature of the amine. For strongly basic amines (e.g. aniline, $pK_a = 4.6$) the inequality $[H^+] \gg K_a$ applies even at low acidities whereas for weak bases such as 2,4-dinitroaniline the inequality $[H^+] \ll K_a$ applies even at very high acid concentrations. Thus, the two limiting forms are 2.5 and 2.6 :

$$k_o = k_3K_a[ArNH_2]_T \qquad (2.5)$$

$$k_o = k_3[ArNH_2]_T[H^+] \qquad (2.6)$$

It can be seen that acid catalysis should only result when $[H^+] \ll K_a$ and plots of k_o vs $[H^+]$ are expected to be linear. In between these two extremes one would expect a plot of k_o vs $[H^+]$ to curve and reach a limiting value as the transition from 2.6 to 2.5 takes place, and this behaviour has been observed experimentally for many substrates[5].

The following sections describe the results obtained for the substrates mentioned.

2.3 2,4-Dinitroaniline

Due to the low water solubility of this amine it was necessary to carry out the reactions with nitrous acid in excess to achieve first-order conditions, i.e. $[HNO_2] \gg [ArNH_2]$. Referring back to equation 2.3 we now write :

$$\text{RATE} = k_o[ArNH_2]$$

and so

$$k_o = \frac{k_3 K_a [HNO_2][H^+]}{[H^+] + K_a} \qquad (2.7)$$

which has the same form as 2.4. Under the acidic conditions used in these experiments the ionisation of nitrous acid to nitrite can be neglected, and all of the reactions were so rapid that the spontaneous decomposition of nitrous acid was not a problem.

As mentioned earlier, 2,4-dinitroaniline is a very weak base ($pK_a = -4.5$)[6] and consequently the limiting condition $[H^+] \ll K_a$ applies. 2.7, then, becomes :

$$k_o = k_3[HNO_2][H^+] \qquad (2.8)$$

For this amine acid catalysis is found over the whole range and the form of the catalysis suggests that even at very high acidities diazotisation should proceed rapidly, since no significant protonation is likely to occur until very high acid concentrations are used. Values of k_o obtained are presented in table 2.1 and shown graphically in figure 2.1

Table 2.1 ACID CATALYSED DIAZOTISATION OF 2,4-DINITROANILINE

$[Amine] = 1.48 \times 10^{-5}M$ $[HNO_2] = 5.44 \times 10^{-2}M$ $\lambda = 410nm$

$[H^+]/M$	$10^2 k_o/s^{-1}$
0.260	4.38 ± 0.419
0.360	5.86 ± 0.228
0.500	8.87 ± 0.316
0.735	18.0 ± 0.199
0.998	33.0 ± 0.311

At acidities greater than about 0.5M H^+ it is more appropriate to use an acidity function rather than acid concentration as a measure of acidity[7]. This requirement accounts for the upward curvature of of the plot in figure 2.1, but unfortunately no acidity function for

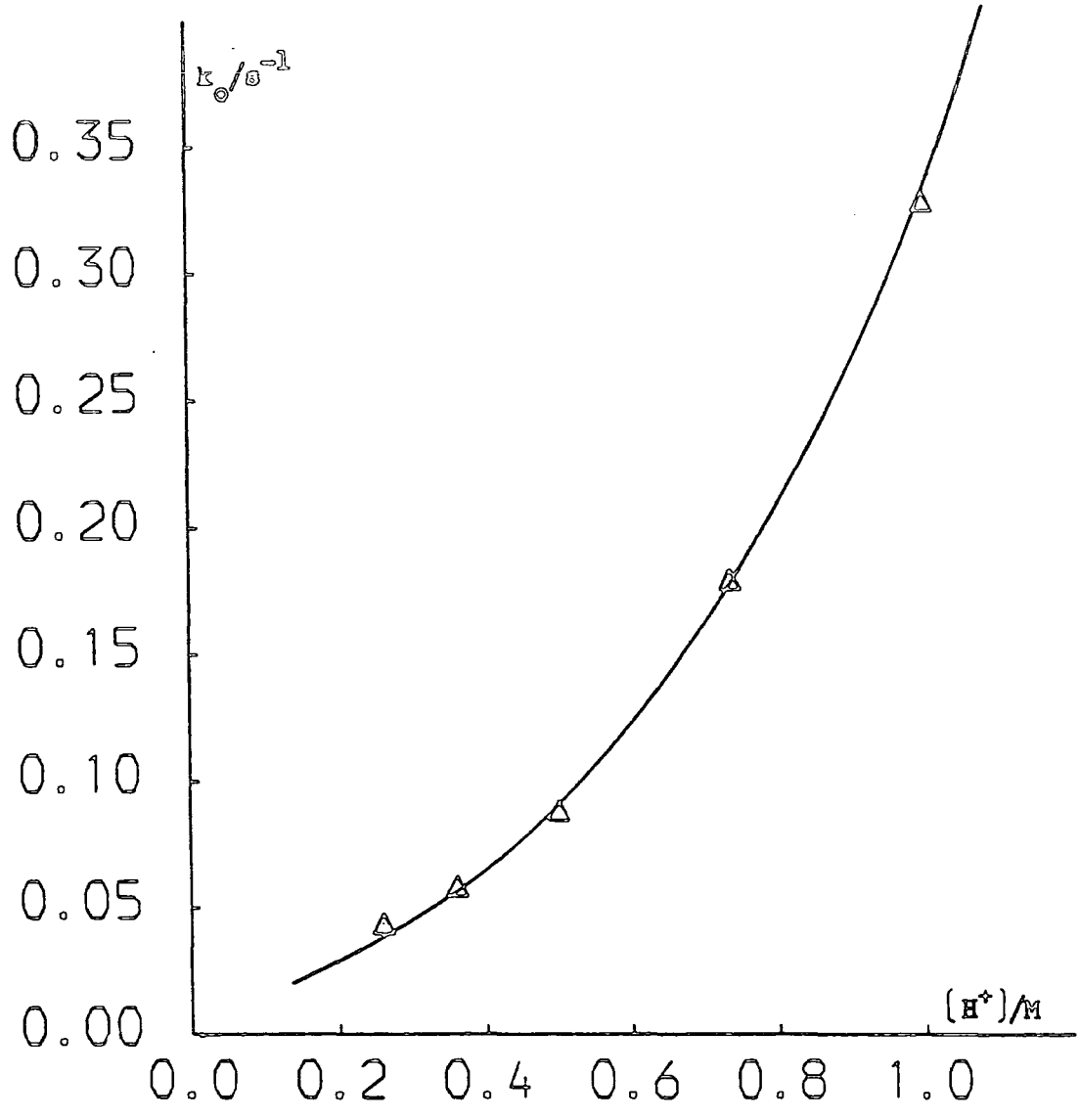

FIG. 2.1 — Acid Catalysed Diazotisation of 2,4-Dinitroaniline

protonation of nitrous has been evaluated.

Assuming a linear $[H^+]$ dependence at low acidity, it is possible to evaluate the third-order rate constant k_3 at 25°C. From the graph:

$$\text{SLOPE} = k_3[HNO_2] = 0.155\ M^{-1}s^{-1}$$

which gives a value for k_3 of 2.5 $dm^6mol^{-2}s^{-1}$ at 25°C. Using this value and the value of 0.37 determined at 0°C by Larkworthy[¤], the activation energy for this reaction is calculated to be 52kJmol^{-1}.

2.4 4-Nitroaniline.

As with 2,4-dinitroaniline, solubility problems necessitated the use of an excess of nitrous acid over the amine to achieve first-order conditions and so the equations of the previous section apply here also.

The K_a value[6] for 4-nitroaniline is 0.1 and so neither of the limiting forms apply since K_a is comparable with (and at one point equal to) the acid concentration over the range studied (up to 0.5M). Therefore, for this amine of intermediate basicity, equation 2.7 predicts that the plot of k_o vs $[H^+]$ will curve to a limiting value but just fall short of it. This behaviour was found experimentally as illustrated in figure 2.2. The non-linearity of this plot prevents the direct determination of k_3. If, however, the reciprocal of equation 2.7 is used then an equation of the form $y = mx + c$ is obtained:

¤ Ref. 1. An error has resulted in the value being reported as 3.7 $dm^6mol^{-2}s^{-1}$ in the original paper. The correct value is 0.37 $dm^6mol^{-2}s^{-1}$.

$$\frac{1}{k_o} = \frac{1}{k_3[HNO_2][H^+]} + \frac{1}{k_3 K_a [HNO_2]} \qquad (2.9)$$

Thus, a plot of k_o^{-1} vs $[H^+]^{-1}$ will result in a straight line and k_3 can be determined from the slope. When applying this treatment it is important to bear in mind the fact that small errors in the original kinetic data may lead to considerable errors in the slope and intercept of the reciprocal plot. For this reason a method of statistical weighting should be applied to the data. The method used here and in the following chapters was weighted least-squares linear regression analysis[8] as described in detail in chapter 6.

Table 2.2 ACID CATALYSED DIAZOTISATION OF 4-NITROANILINE

$[Amine] = 5.52 \times 10^{-5}M$ $[HNO_2] = 5.18 \times 10^{-2}M$ $\lambda = 245nm$

$[H^+]/M$	k_o/s^{-1}
0.0964	6.68 ± 0.168
0.241	8.63 ± 0.115
0.482	10.6 ± 0.193
0.732	11.6 ± 0.310
0.964	12.3 ± 0.345

Evidently, the rate constant k_3 can also be evaluated using the intercept of the reciprocal plot, but this requires a knowledge of

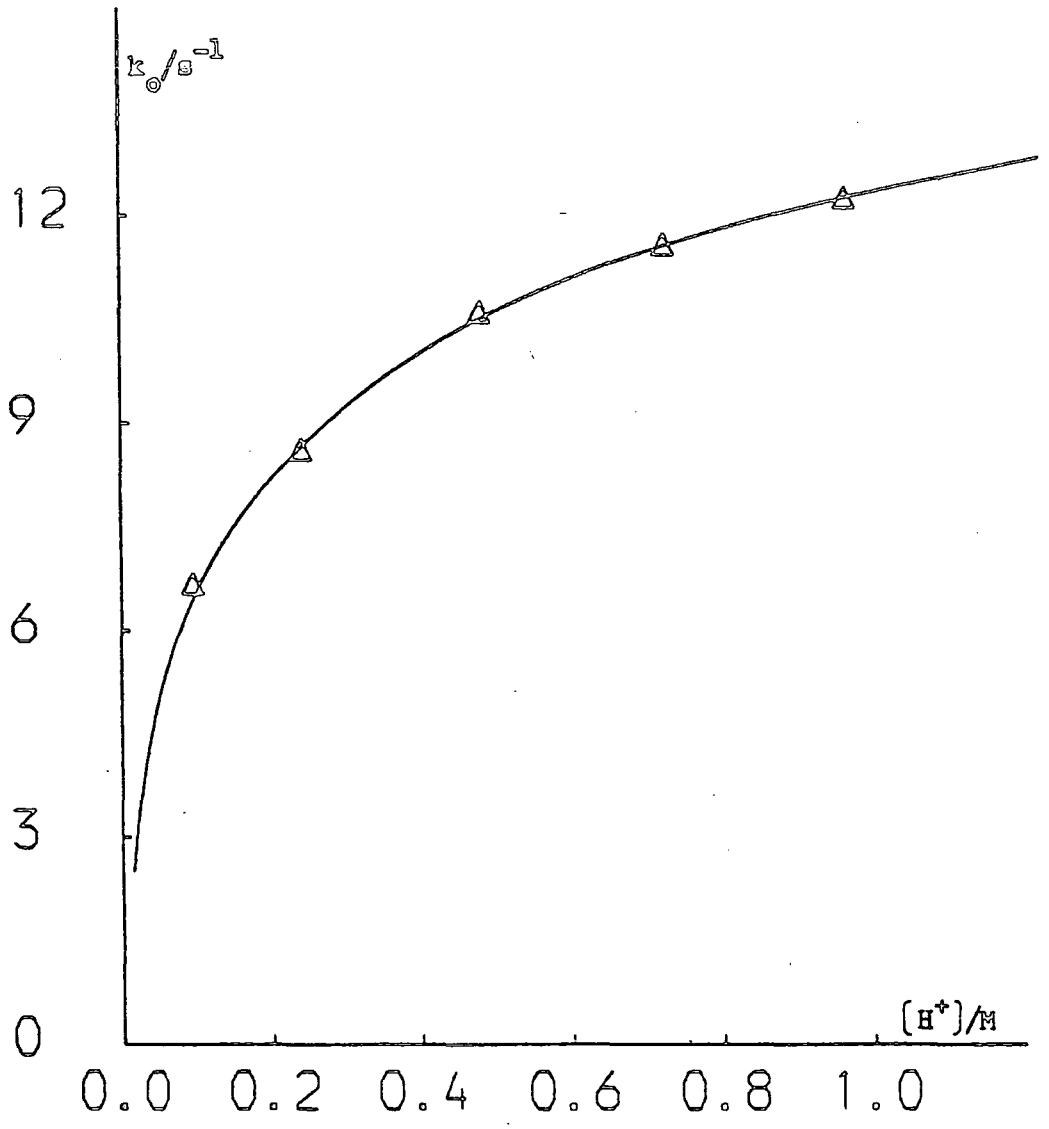

FIG. 2.2 — Acid Catalysed Diazotisation of 4-Nitroaniline

the K_a value for the amine under consideration. Alternatively, the intercept provides a means of determining previously unknown or untrustworthy K_a values for amines which exhibit this non-linear acid dependence. The K_a value for 4-nitroaniline has been determined by many workers[6] and the value of 0.1 is now well established. This value, then, provides a means of checking the usefulness of equation 2.9 for determining K_a values. The calculated slope of the reciprocal plot (figure 2.3) yields a third-order rate constant value of 2.71×10^3 $dm^6 mol^{-2} s^{-1}$ at 25°C and from the intercept $K_a = 0.092$ mol dm^{-3}, which is in excellent agreement with the literature value[6].

Table 2.3 4-NITROANILINE H^+ RECIPROCAL DATA

$[H^+]^{-1}/M^{-1}$	k_o^{-1}/s
10.4	0.150
4.15	0.116
2.07	0.0942
1.38	0.0862
1.04	0.0814

SLOPE = 7.12×10^{-3} mol dm^{-3} s

INTERCEPT = 7.71×10^{-2} s

(SLOPE and INTERCEPT calculated using weighted least-squares linear regression analysis).

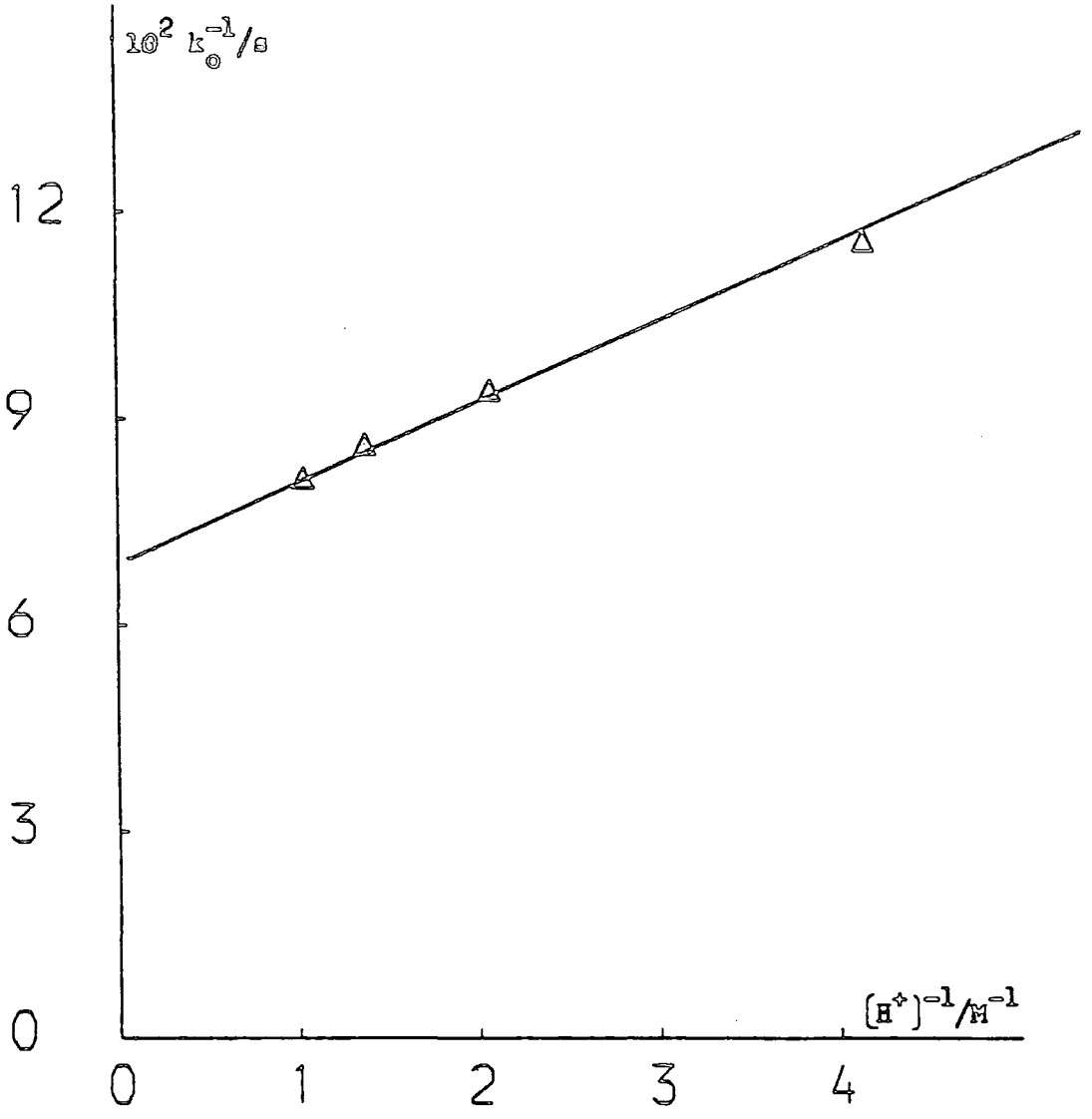

Fig. 2.3

4-Nitroaniline - Acid Reciprocal Data

The activation energy calculated using the above rate constant and that obtained at 0°C by Larkworthy[1] was 76 kJ mol^{-1}.

2.5 Sulphanilamide

The dependence of the reaction rate on the concentration of sulphanilamide is shown in table 2.4 and graphically in figure 2.4, indicating that the order with respect to sulphanilamide is unity.

Table 2.4 SULPHANILAMIDE SUBSTRATE DEPENDENCE

$10^3 \times [Amine]/M$	$10^2 \times k_o/s^{-1}$
0.631	1.20 ± 0.035
1.26	2.36 ± 0.052
3.16	6.05 ± 0.15
6.31	12.3 ± 0.27

The reasonably high water solubility of this amine allowed the use of low nitrous acid concentrations to achieve first-order conditions i.e. $[HNO_2] \ll [ArNH_2]$. No data on the diazotisation of this amine seem to be available in the literature other than a comparison between diazotisation by nitrous acid and by an alkyl nitrite[9].

As for 4-nitroaniline, the plot of k_o vs $[H^+]$ curved off and in this case a limiting value of k_o was reached at about 0.3M H^+. The double reciprocal plot obtained from the data was used to determine the

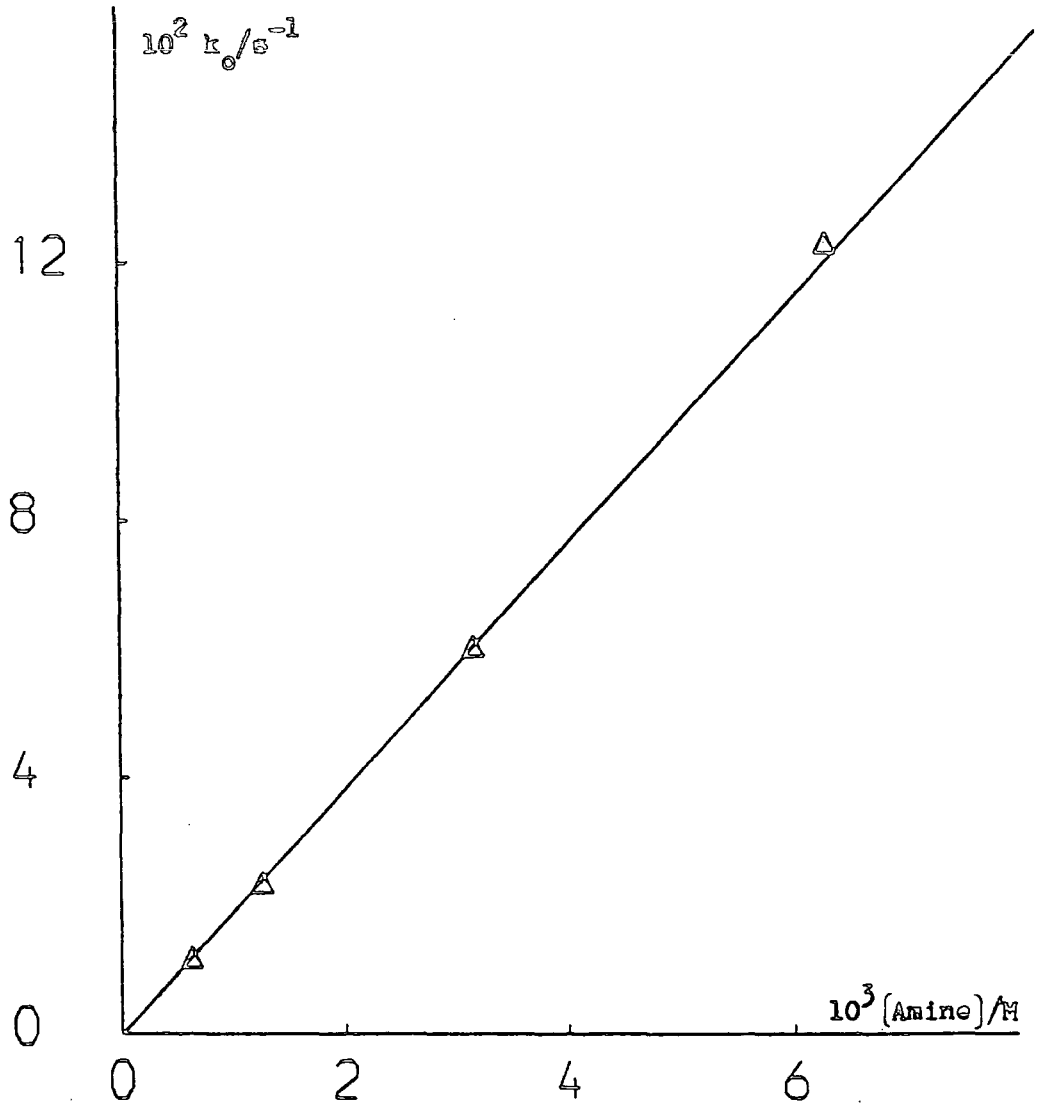

FIG. 2.4 — Sulphanilamide Substrate Dependence

pK_a value for sulphanilamide in the same manner as for 4-nitroaniline. Literature values[6] lie in the range 2.0-2.3, whereas the present method yielded a value of 1.4. In view of the fact that this method has yielded pK_a values for other substrates which are in excellent agreement with well established literature values - e.g. sulphamic acid[10], urea[11], and 4-nitroaniline above - the present value can be accepted with some confidence, despite the poor agreement with previous ones. Inspection of the k_o vs $[H^+]$ plot and consideration of equation 2.4 shows that if the pK_a value were, say, 2.0 ($K_a = 0.01$) then the plot should level off at a much lower acid concentration. The third-order rate constant k_3 can be evaluated using equation 2.10, which is the equivalent of 2.9 under the present conditions, and the calculated slope of the reciprocal plot. The value obtained in this way was 9.00×10^2 dm^6 mol^{-2} s^{-1} at 25°C. The intercept yields a value of 3.77×10^{-2} mol dm^{-3} for K_a. Using the limiting value of k_o (taken as 0.236 s^{-1}) and equation 2.5 a value of 3.62×10^{-2} mol dm^{-3} is obtained for K_a.

$$\frac{1}{k_o} = \frac{1}{k_3[ArNH_2]_T[H^+]} + \frac{1}{k_3 K_a [ArNH_2]_T} \qquad (2.10)$$

Table 2.5 ACID CATALYSED DIAZOTISATION OF SULPHANILAMIDE

$[ArNH_2] = 6.39 \times 10^{-3}M$ · $[HNO_2] = 5.18 \times 10^{-5}M$ $\lambda = 310nm$

$10 \times [H^+]/M$	$10 \times k_o/s^{-1}$
0.237	0.950 ± 0.018
0.474	1.29 ± 0.033
0.948	1.67 ± 0.046
1.42	1.98 ± 0.14
1.90	2.05 ± 0.027
3.30	2.31 ± 0.19
4.18	2.33 ± 0.20
5.21	2.36 ± 0.033
9.64	2.45 ± 0.087

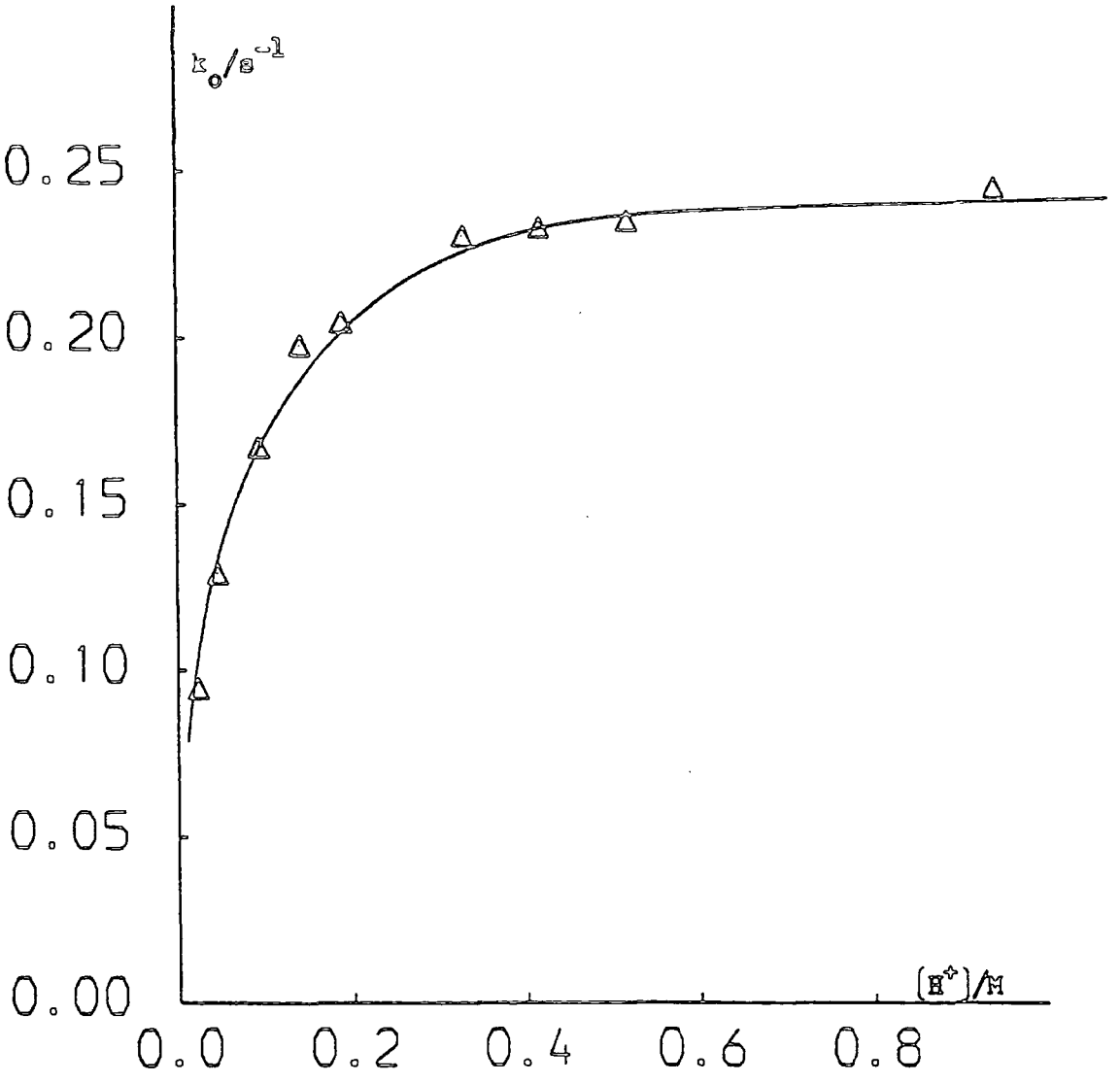

FIG. 2.5 — Acid Catalysed Diazotisation of Sulphanilamide

Table 2.6 SULPHANILAMIDE RECIPROCAL DATA

$[H^+]^{-1}/M^{-1}$	k_o^{-1}/s
42.2	10.5
21.1	7.73
10.6	5.97
7.03	5.05
5.28	4.88
3.03	4.33
2.39	4.21
1.98	4.25
1.04	4.08

SLOPE = 0.154 mol dm^{-3} s

INTERCEPT = 4.09 s

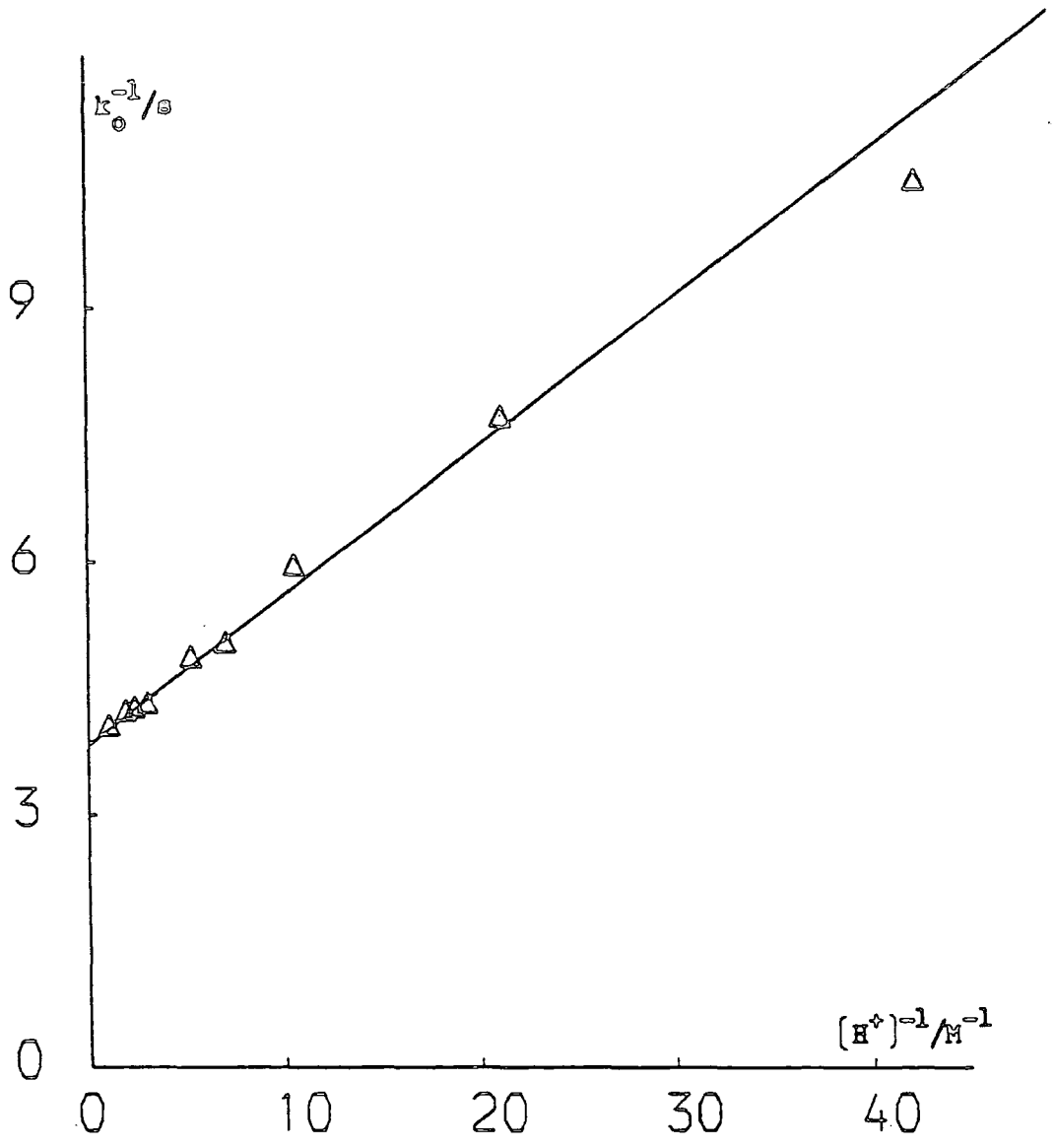

FIG. 2.6 — Sulphanilamide Acid Reciprocal Data

2.6 Sulphanilic acid

Again, the variation of reaction rate with substrate concentration indicates that the order with respect to sulphanilic acid is unity. The results are presented below.

Table 2.7 SULPHANILIC ACID SUBSTRATE DEPENDENCE

10^2 x [Amine]/M	10^2 x k_o/s^{-1}
1.22	0.530 ± 0.012
2.45	1.05 ± 0.072
6.12	2.63 ± 0.077
12.3	4.71 ± 0.096

This amine has been much used as a nitrous acid trap - a consequence of the irreversibility of diazotisation - and also synthetically in the production of azo-dyes. Methyl Orange, for example, is diazotised sulphanilic acid coupled with N,N-dimethylaniline[12]. No data on the kinetics of diazotisation of this amine were found in the literature.

The relatively large pK_a value[6] for sulphanilic acid (3.2) means that the inequality $[H^+] \gg K_a$ applies at all but the very lowest acidities ($\sim 10^{-2}$M) and so no acid catalysis should be observed over the acidity range studied, and a horizontal plot of k_o vs $[H^+]$ should

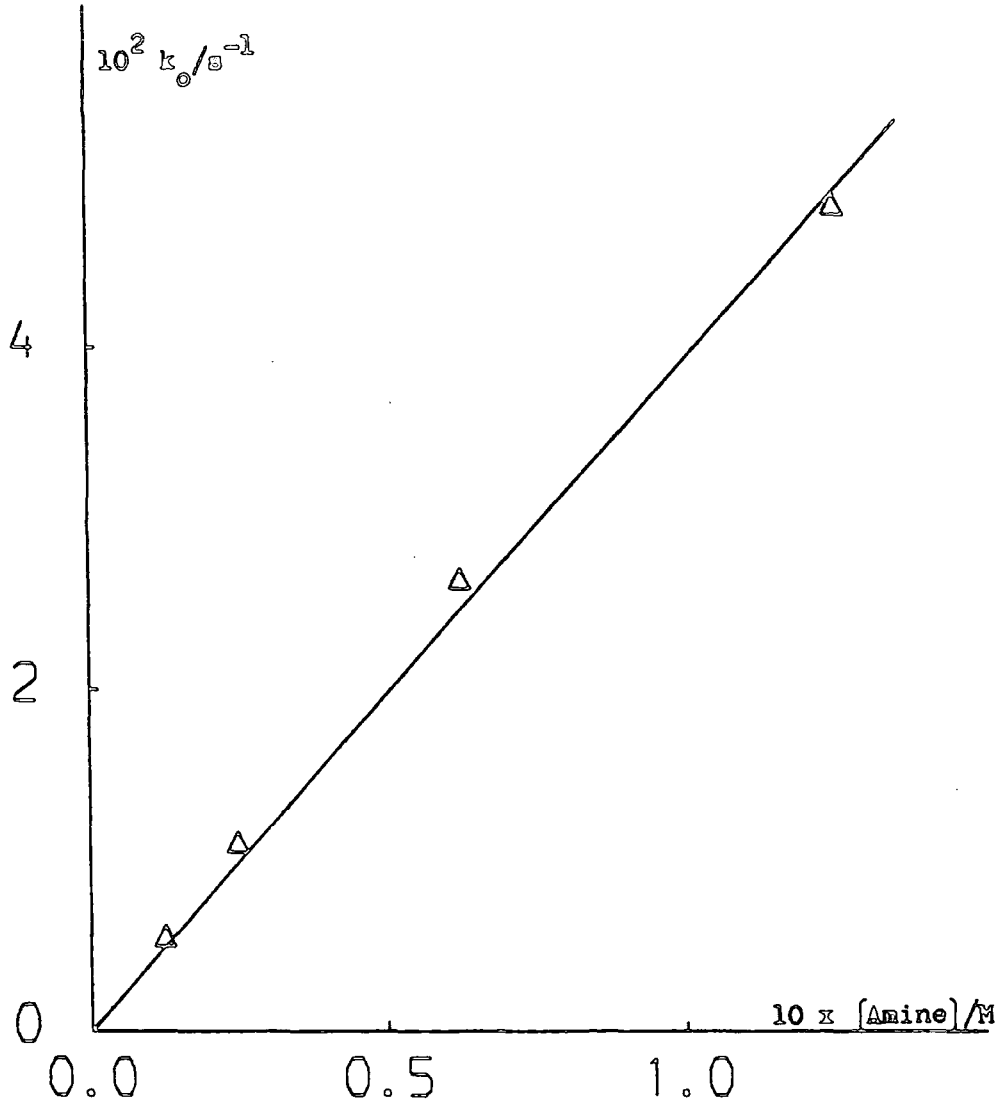

FIG. 2.7 — Sulphanilic Acid Substrate Dependence

be obtained. This was observed experimentally up to about 0.1M H^+ but above this acid concentration the plot curved upwards as occurred in the case of 2,4-dinitroaniline. This is shown in figure 2.8. As mentioned earlier, it is more appropriate to use an acidity function rather than $[H^+]$ as a measure of acidity. It is possible here to use the Hammett acidity function[7] h_o since this was originally evaluated using aniline derivatives[13], and sulphanilic acid is a typical 'Hammett Base'. The plot of k_o vs h_o is shown in figure 2.9.

This extended catalysis has been interpreted for aniline derivatives in terms of another mechanistic pathway involving nitrosation of the protonated amine in which NO^+ is bound initially to the aromatic ring[14]. This mechanism was explained in section 1.3 and is shown in scheme 1.5, page 11.

For the additional catalysis we have :

$$\text{RATE} = k_3'[ArNH_3^+][HNO_2]h_o$$

and since $$[ArNH_2]_T = [ArNH_3^+] + [ArNH_2]_F$$

and $$K_a = \frac{[ArNH_2]h_o}{[ArNH_3^+]}$$

we have $$\text{RATE} = \frac{k_3'[ArNH_2]_T h_o^2[HNO_2]}{h_o + K_a}$$

and since $h_o \gg K_a$ for all h_o in the range, this becomes:

$$k_o = k_3^o(ArNH_2)_T h_o$$

and the linear h_o dependence is predicted. The value of k_3^o, determined using the slope of this line, was 2.5 $dm^6 mol^{-2} s^{-1}$ at 25°C. Taking the intercept of the plot to represent the limiting value of k_o, the third order rate constant k_3 for reaction of the non-protonated amine was evaluated using equation 2.5 as 7.3×10^3 $dm^6 mol^{-2} s^{-1}$ at 25°C. This illustrates the large difference in the reactivity between the protonated and non-protonated forms of the amine.

Table 2.8 ACID CATALYSED DIAZOTISATION OF SULPHANILIC ACID

$[Amine] = 1.23 \times 10^{-2}$M $[HNO_2] = 5.30 \times 10^{-5}$M $\lambda = 300$nm

$10^2 \times [H^+]$/M	$10^2 \times k_o/s^{-1}$
0.964	5.44 ± 0.14
9.64	5.68 ± 0.045
48.2	6.94 ± 0.20
96.4	10.1 ± 0.11
145	15.8 ± 2.6
193	22.7 ± 1.4

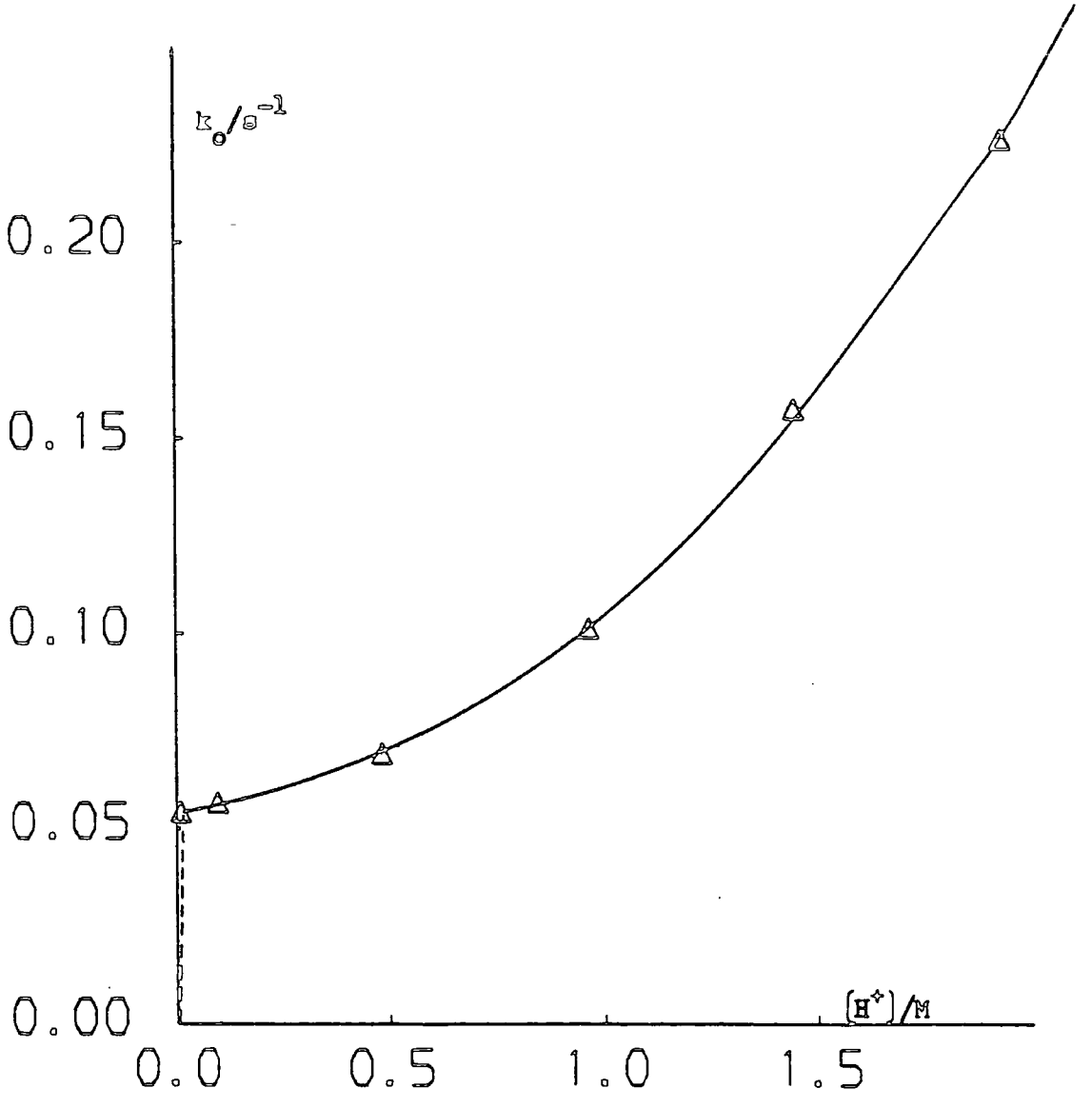

FIG. 2.8 — Acid Catalysed Diazotisation of Sulphanilic Acid

Table 2.9 SULPHANILIC ACID h_o DEPENDENCE

$10^2 \times h_o$	$10^2 \times k_o/s^{-1}$
0.964	5.44
9.64	5.68
60.0	6.94
163	10.1
338	15.8
568	22.7

SLOPE = 0.0307

INTERCEPT = 0.0529

2.7 Conclusion

The third-order rate constants obtained at 25°C for the diazotisation of the substrates under consideration in this chapter are presented in table 2.10 together with the respective pK_a values.

Amine	$k_3/dm^6 mol^{-2} s^{-1}$	pK_a
2,4-dinitroaniline	2.5	-4.5
4-nitroaniline	2.7×10^3	1.0
sulphanilamide	9.0×10^2	1.4
sulphanilic acid	7.3×10^3	3.2

Table 2.10

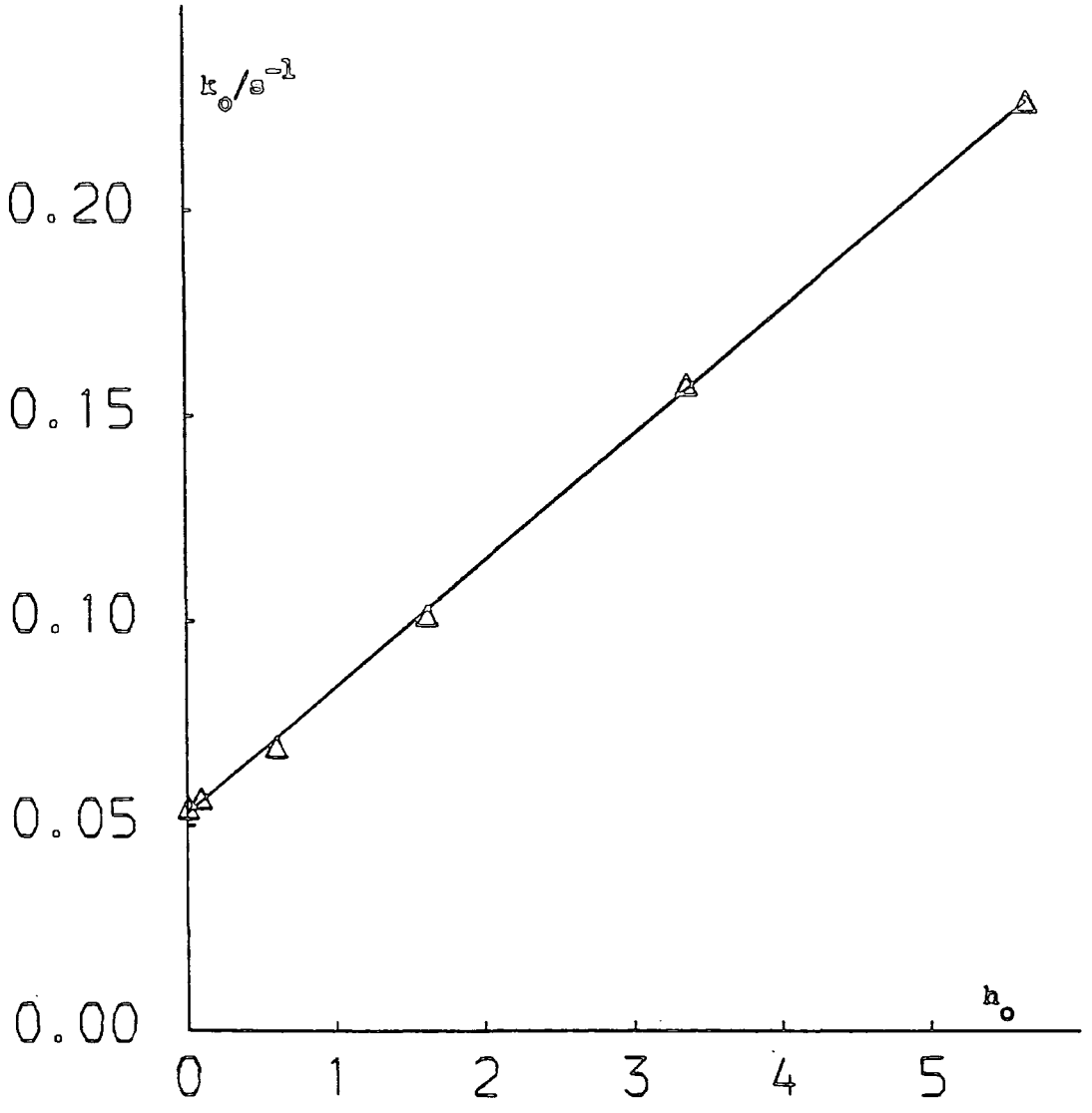

FIG. 2.9 — Sulphanilic Acid, h_o dependence

For all of these substrates the expected behaviour was observed i.e. from inspection of equation 2.4 (or the similar form 2.7) and consideration of the K_a value for each substrate the approximate shape of each plot could be predicted, with the exception perhaps of the extended catalysis for sulphanilic acid. The low reactivity of 2,4-dinitroaniline can be attributed to the deactivating effect of the nitro groups which reduce the amine's strength as a nucleophile. For the more basic amines the rate constants are of similar magnitude and it is thought that rate constants of this order are close to the diffusion controlled limit for this process[15]. The value of k_3 for sulphanilic acid is one of the largest reported at 25°C and contrasts with the much lower value obtained for reaction of the protonated form of the amine.

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CHAPTER 3

NUCLEOPHILE CATALYSIS in the DIAZOTISATION of ANILINE DERIVATIVES

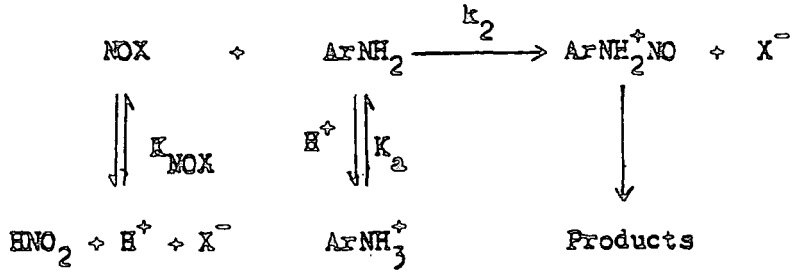
3.1 Introduction

The data presented in this chapter describe the nucleophile catalysed diazotisation of the aniline derivatives considered in chapter 2 and are an extension of that work. Catalysis by chloride, bromide, iodide, thiocyanate, and thiourea were studied for both sulphanilic acid and sulphanilamide. For 2,4-dinitroaniline, only catalysis by bromide and thiocyanate was studied, as described later. The nucleophile catalysed diazotisation of 4-nitroaniline has been studied previously[1] and the rate constants obtained in that work will be presented for comparison purposes.

The reaction conditions were as described in 2.1 and chapter 6 and a full account of the analytical methods and treatment of results can be found in chapter 6.

3.2 Derivation of the General Rate Equation.

Catalysis by the general nucleophile X^- occurs via the formation of a covalent nitrosyl compound, NOX, which attacks the lone pair of electrons on the nitrogen atom[2]. The reaction scheme is shown below.



SCHEME 3.1

The rate-determining step in this scheme is attack of NOX generally[2], unless the reaction conditions are such that formation of NOX or proton loss is rate controlling, as described in chapter 1. For rate-determining nitrosation, then, we have :

$$\text{RATE} = k_2[ArNH_2][NOX] \qquad (3.1)$$

where the concentrations are molecular concentrations. We can derive an expression for $[ArNH_2]$ as in chapter 2, and using the expression for K_{NOX} we can replace $[NOX]$ in the above equation :

$$K_{NOX} = \frac{[NOX]}{[HNO_2][H^+][X^-]}$$

$$\text{also} \qquad [HNO_2]_T = [HNO_2]_F + [NOX]$$

where, as before, the subscripts T and F refer to total (stoichiometric) and free (molecular) concentrations respectively. Combining these two expressions gives :

$$[HNO_2]_F = \frac{[HNO_2]_T}{(1 + K_{NOX}[H^+][X^-])}$$

and, after substitution of $K_{NOX}[HNO_2][H^+][X^-]$ for $[NOX]$ in equation 3.1, we have :

$$\text{RATE} = \frac{k_2[ArNH_2]_T[HNO_2]_T[H^+][X^-]K_aK_{NOX}}{([H^+] + K_a)(1 + K_{NOX}[H^+][X^-])} \qquad (3.2)$$

Under first-order conditions ($[ArNH_2] \gg [HNO_2]$), the observed first-order rate constant is defined by :

$$-\frac{d[HNO_2]}{dt} = k_o[HNO_2]$$

Hence :

$$k_o = \frac{k_2[ArNH_2]_T[H^+][X^-]K_aK_{NOX}}{([H^+] + K_a)(1 + K_{NOX}[H^+][X^-])} \qquad (3.3)$$

Since these reactions were carried out under acidic conditions, reaction via NOX is accompanied by a reaction via $H_2NO_2^+$ and so 3.3 will also include a term in this uncatalysed reaction. This term was derived in chapter 2 and leads to :

$$k_o = \frac{k_2[ArNH_2][H^+][X^-]K_aK_{NOX}}{([H^+] + K_a)(1 + K_{NOX}[H^+][X^-])} + \frac{k_3[ArNH_2][H^+]K_a}{([H^+] + K_a)}$$

Since this second term is constant for a given reaction under the conditions used in the following studies, it will be omitted from the following rate expressions for convenience. It will be referred to when necessary in the manipulation of the above equation and when considering plots of k_o vs $[X^-]$.

The following sections describe the evaluation of the bimolecular rate constants k_2, for reaction of various NOX species, using equation 3.3.

3.3 Halide Ion Catalysis

As a consequence of the low values of the equilibrium constants for formation of NOCl and NOBr (1.1×10^{-3} and 5.1×10^{-2} $mol^{-2}dm^{6}$ respectively[3,4] at 25°C), the inequality

$$1 \gg K_{NOX}[H^+][X^-]$$

is applicable across the range of $[X^-]$ used in this work. Hence, equation 3.3 becomes :

$$k_o = \frac{k_2[ArNH_2]_T[H^+][X^-]K_a K_{NOX}}{([H^+] + K_a)} \qquad (3.4)$$

and one would expect a linear dependence of k_o upon $[X^-]$. The results obtained for diazotisation of sulphanilic acid and sulphanilamide catalysed by chloride, bromide, and iodide are presented in the following tables and shown graphically in figures 3.1-3.4.

Table 3.1 SULPHANILIC ACID CHLORIDE CATALYSIS

$[ArNH_2]_T = 1.22 \times 10^{-2}M$ $[HNO_2] = 5.02 \times 10^{-5}M$ $[H^+] = 3.58 \times 10^{-2}M$

$10^2 \times [Cl^-]/M$	k_o/s^{-1}
2.50	0.382 ± 0.012
5.00	0.708 ± 0.025
7.49	0.963 ± 0.052
9.99	1.26 ± 0.048

SLOPE = 11.5 $dm^3 mol^{-1} s^{-1}$

INTERCEPT = 0.107 s^{-1}

Table 3.2 SULPHANILIC ACID BROMIDE CATALYSIS

$[ArNH_2]_T = 1.22 \times 10^{-2}M$ $[HNO_2] = 5.02 \times 10^{-5}M$ $[H^+] = 3.58 \times 10^{-2}M$

$10^2 \times [Br^-]/M$	k_o/s^{-1}
2.50	7.19 ± 0.041
5.00	11.5 ± 0.20
7.50	14.6 ± 0.055
10.0	17.0 ± 0.11

Table 3.3 SULPHANILIC ACID IODIDE CATALYSIS

$[ArNH_2]_T = 1.22 \times 10^{-2}$M $[HNO_2] = 5.40 \times 10^{-5}$M $[H^+] = 3.58 \times 10^{-2}$M

$10^3 \times [I^-]/M$	k_o/s^{-1}
1.01	0.687 ± 0.019
2.02	1.36 ± 0.032
3.03	1.94 ± 0.027
4.04	2.57 ± 0.046

SLOPE = 618 $dm^3 mol^{-1} s^{-1}$

INTERCEPT = 7.87×10^{-2} s^{-1}

Table 3.4 SULPHANILAMIDE CHLORIDE CATALYSIS

$[ArNH_2]_T = 6.39 \times 10^{-3}$M $[HNO_2] = 5.02 \times 10^{-5}$M $[H^+] = 4.16 \times 10^{-2}$M

$10^2 \times [Cl^-]/M$	k_o/s^{-1}
2.50	1.14 ± 0.06
5.00	1.97 ± 0.08
7.50	2.76 ± 0.11
10.0	3.50 ± 0.17

SLOPE = 31.3 $dm^3 mol^{-1} s^{-1}$

INTERCEPT = 0.382 s^{-1}

Table 3.5 SULPHANILAMIDE BROMIDE CATALYSIS

$[ArNH_2] = 6.39 \times 10^{-3}M$ $[HNO_2] = 5.02 \times 10^{-5}M$ $[H^+] = 4.16 \times 10^{-2}M$

$10^2 \times [Br^-]/M$	k_o/s^{-1}
2.50	6.79 ± 0.19
5.00	10.7 ± 0.096
7.50	13.4 ± 0.35
10.0	15.3 ± 0.19

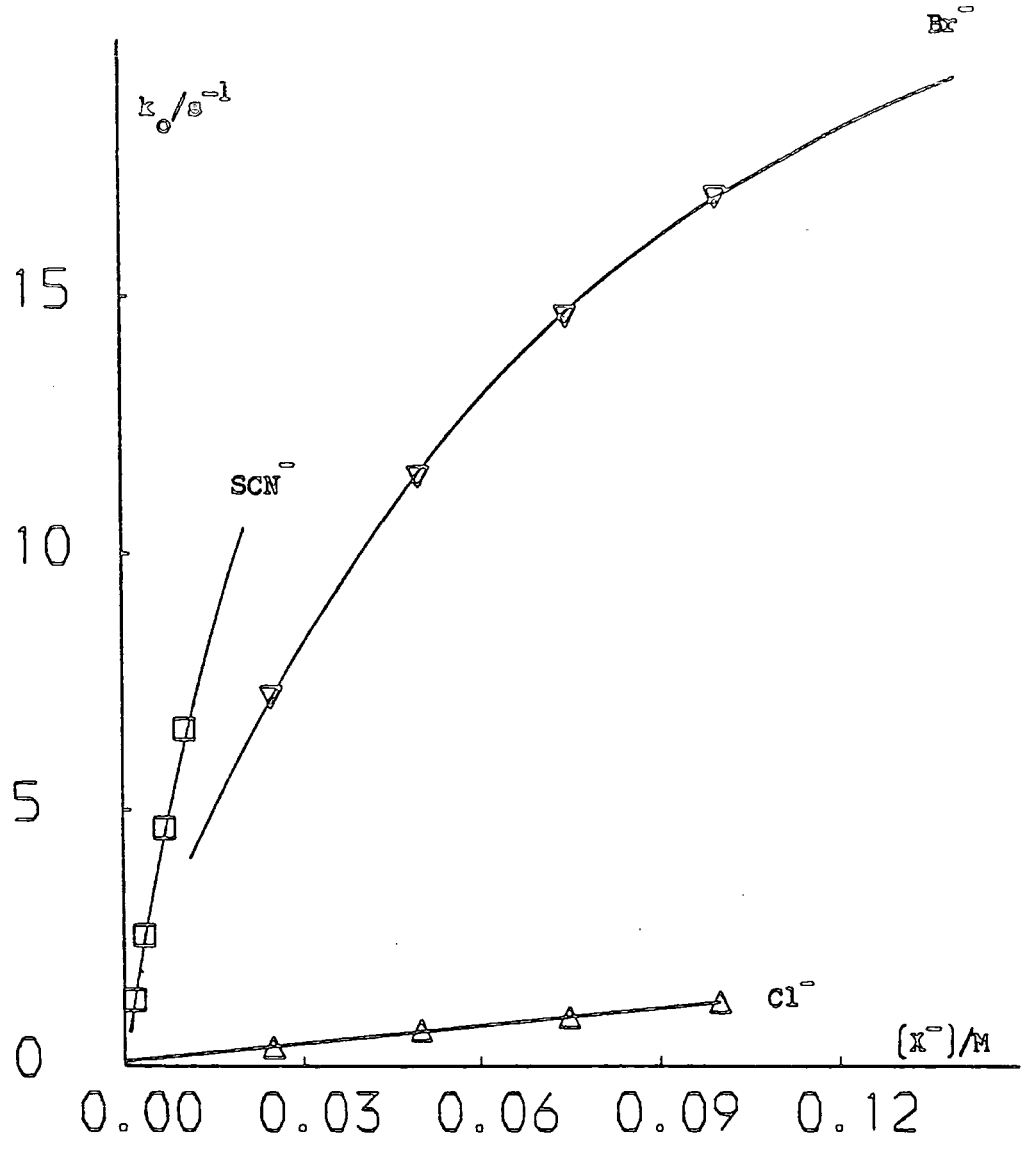
Table 3.6 SULPHANILAMIDE IODIDE CATALYSIS

$[ArNH_2] = 6.39 \times 10^{-3}M$ $[HNO_2] = 5.40 \times 10^{-5}M$ $[H^+] = 4.16 \times 10^{-2}M$

$10^3 \times [I^-]/M$	k_o/s^{-1}
1.01	0.605 ± 0.011
2.02	1.09 ± 0.024
3.03	1.59 ± 0.031
4.04	2.17 ± 0.096

SLOPE = 513 $dm^3 mol^{-1} s^{-1}$

INTERCEPT = 6.60×10^{-2} s^{-1}

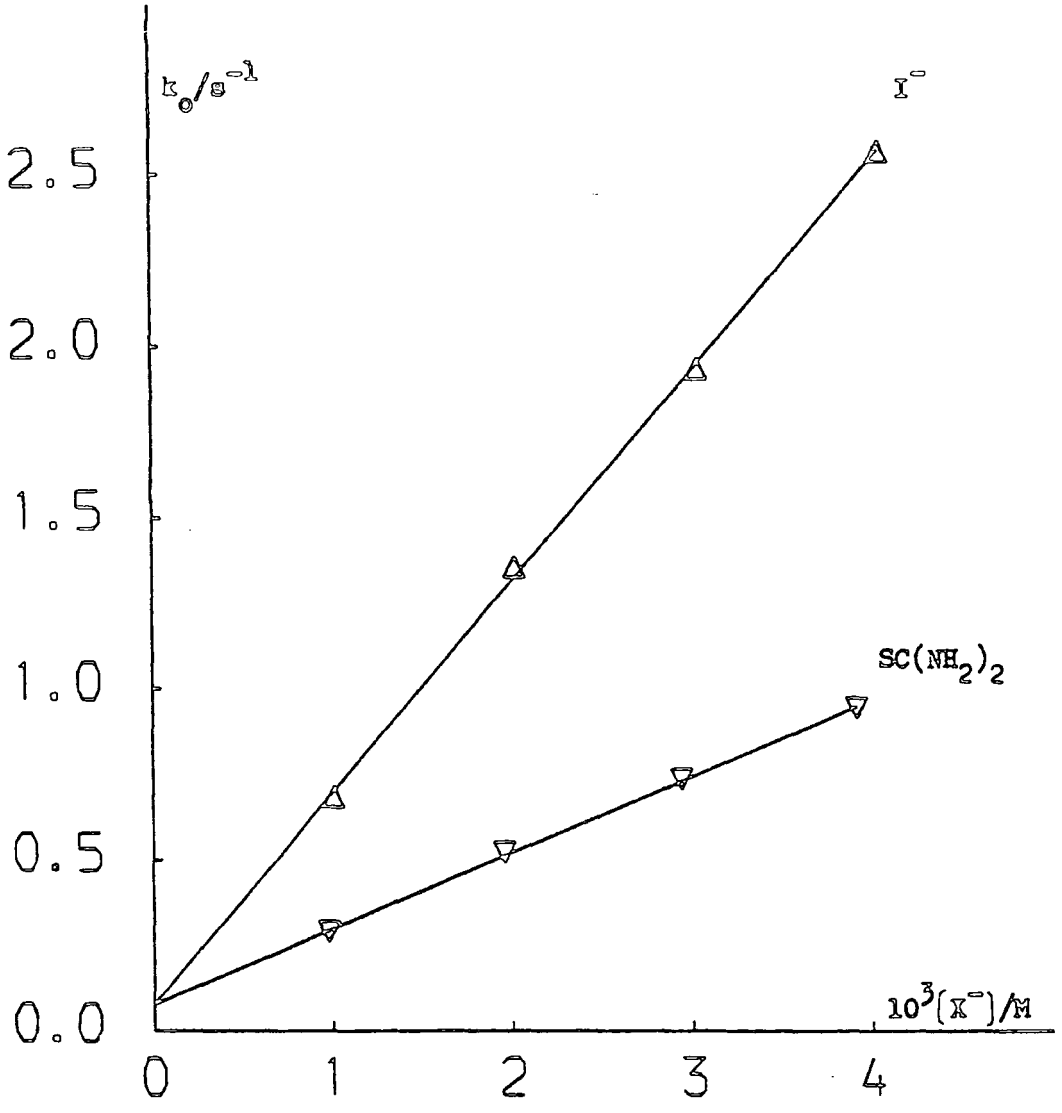


□ Thiocyanate

▽ Bromide

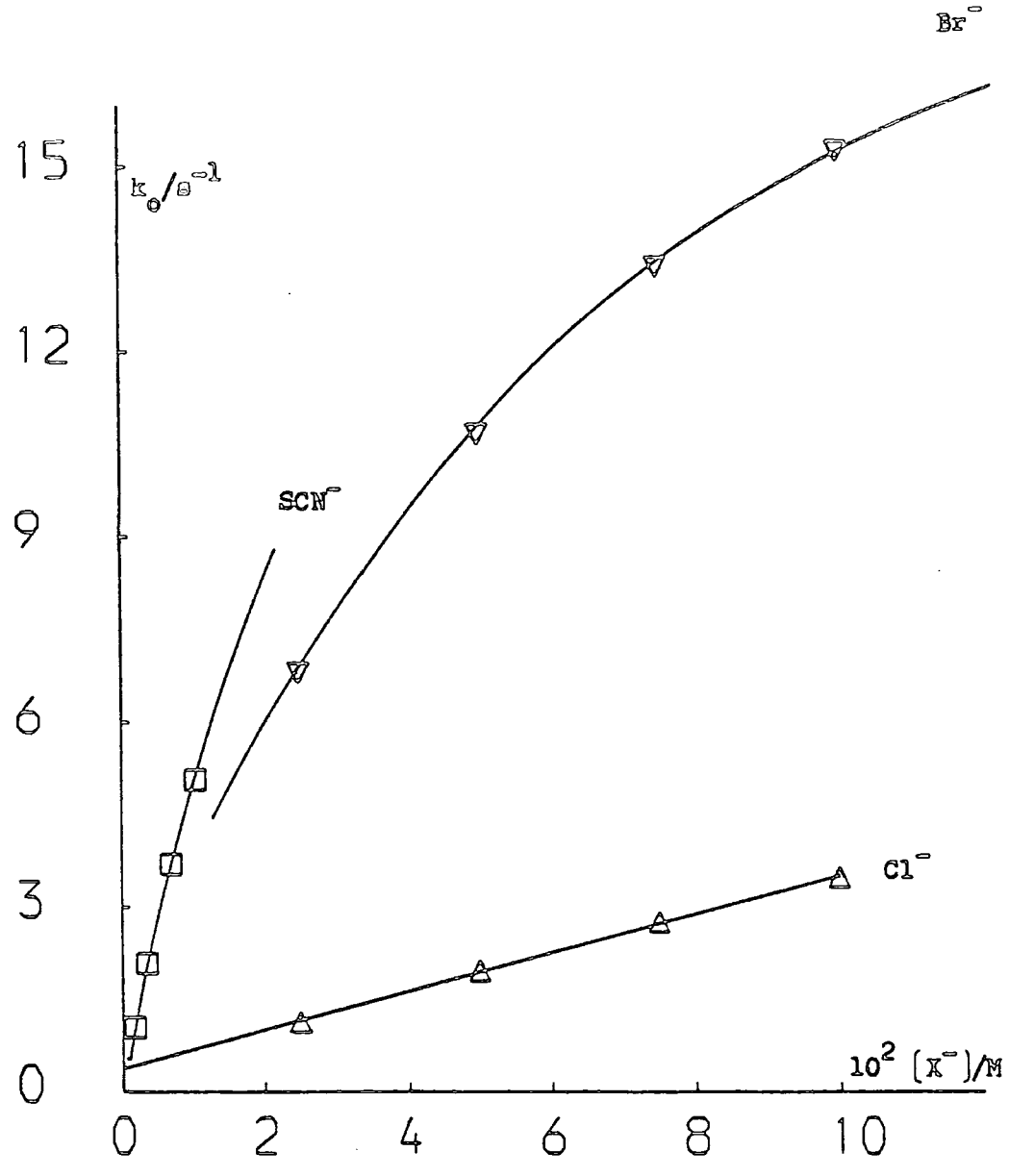
△ Chloride

FIG. 3.1 — Nucleophile Catalysed Diazotisation of Sulphanilic Acid



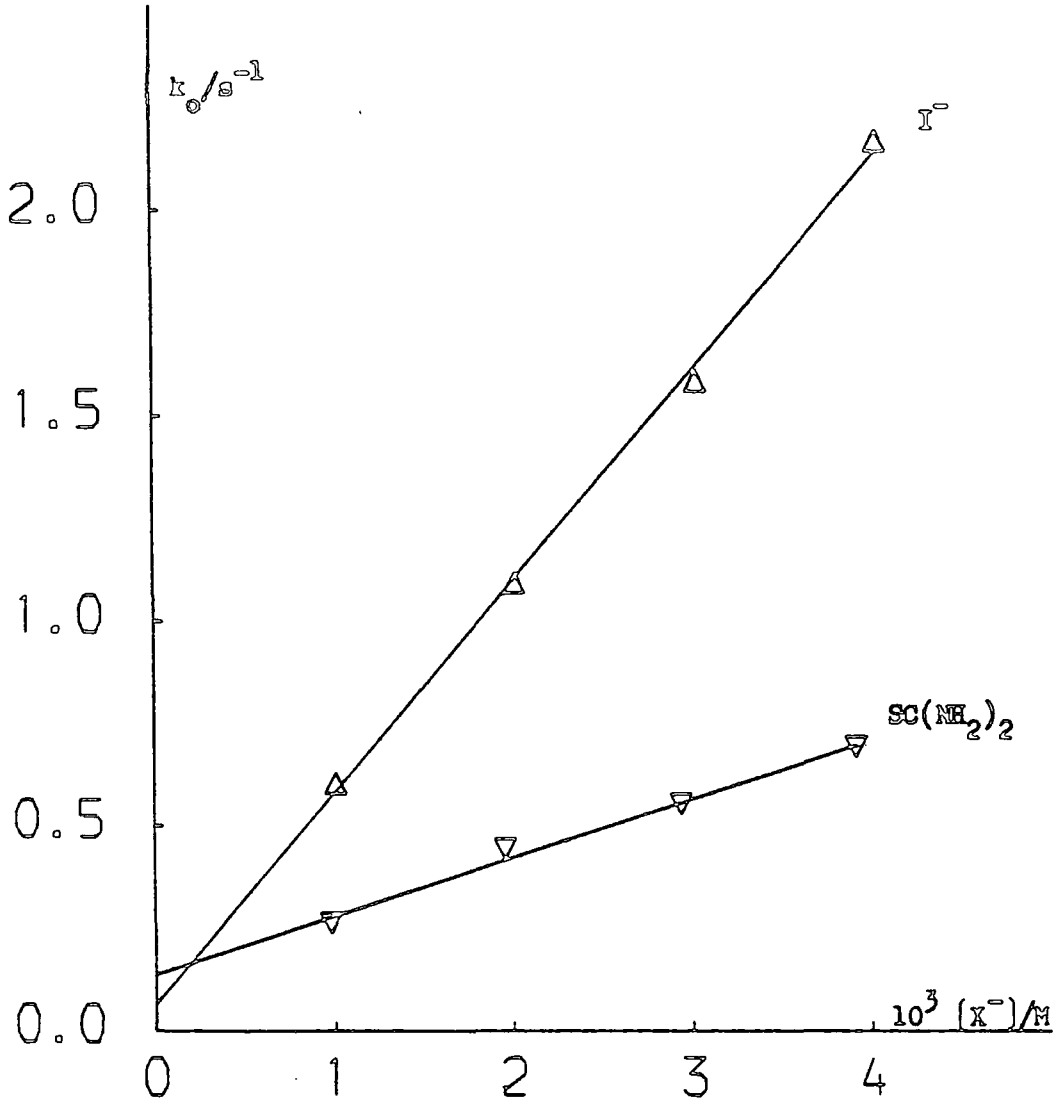
▽ Thiourea
△ Iodide

FIG. 3.2 — Nucleophile Catalysed Diazotisation of Sulphanilic Acid



□ Thiocyanate
▽ Bromide
△ Chloride

FIG. 3.3 — Nucleophile Catalysed Diazotisation of Sulphanilamide



▽ Thiourea
△ Iodide

FIG. 3.4 — Nucleophile Catalysed Diazotisation of Sulphanilamide

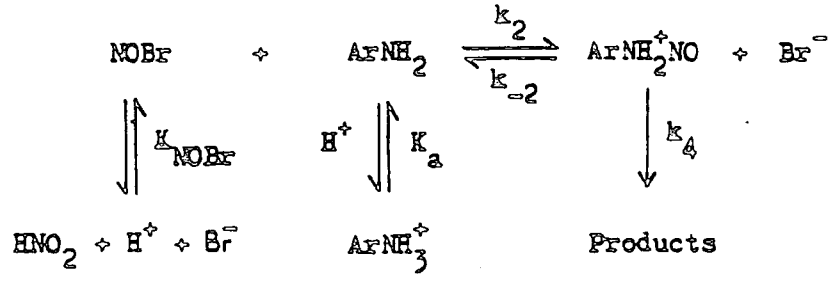
For both substrates plots of k_o vs $[Cl^-]$ are linear, as expected. The linearity of the plots of k_o vs $[I^-]$ suggests that the inequality $1 \gg K_{NOI}[H^+][I^-]$ applies in each case, although the value of the equilibrium constant K_{NOI} is not known.

The slope of each k_o vs $[Cl^-]$ plot is given by:

$$\text{SLOPE} = \frac{k_2[ArNH_2][H^+]K_a K_{NOCl}}{[H^+] + K_a}$$

and the values of k_2 obtained from these were 1.44×10^9 $dm^3mol^{-1}s^{-1}$ and 1.96×10^8 $dm^3mol^{-1}s^{-1}$ for sulphanilic acid and sulphanilamide respectively at 25°C. The qualitative difference between these two values is to be expected since sulphanilic acid is a stronger base and hence more susceptible to electrophilic attack by NOX.

For both substrates the plots of k_o vs $[Br^-]$ were distinctly curved. The low concentrations of bromide ion used rule out the possibility of dominance of $K_{NOBr}[H^+][Br^-]$ in equation 3.3, which would lead to a levelling off of the plot. The curvature is consistent with a mechanism in which the initial rate-determining nitrosation step becomes reversible at higher bromide ion concentrations[1].



SCHEME 3.2

By applying a steady-state approximation to the reactive intermediate $ArNH_2^{\oplus}NO$, the following equation can be derived:

$$k_o = \frac{k_2 k_4 K_a K_{NOBr} [ArNH_2]_T [H^{\oplus}][Br^{\ominus}]}{([H^{\oplus}] + K_a)(k_{-2}[Br^{\ominus}] + k_4)} \qquad (3.5)$$

It is evident from this that the shape of the plot of k_o vs $[Br^{\ominus}]$ depends upon the relative magnitudes of $k_{-2}[Br^{\ominus}]$ and k_4. Two limiting conditions are possible: when $k_{-2}[Br^{\ominus}] \ll k_4$ a linear dependence of k_o on $[Br^{\ominus}]$ is expected, whereas when $k_{-2}[Br^{\ominus}] \gg k_4$ the reaction should be zero-order in $[Br^{\ominus}]$. This behaviour is exhibited by both substrates - the plots of k_o vs $[Br^{\ominus}]$ being linear initially, but tending to level off at higher concentrations of bromide ion. This intermediate situation can be analysed by taking the reciprocal form of equation 3.5 and plotting $(k_o)^{-1}$ vs $[Br^{\ominus}]^{-1}$. Here it must be remembered that 3.5 should include a second term due to the uncatalysed reaction and this must be subtracted from each k_o value before reciprocals are taken. This term, which is numerically equal to the intercept of the k_o vs $[Br^{\ominus}]$ plot, can be calculated as the various constants involved are known. Therefore, denoting the adjusted k_o values as k_o', we have:

$$(k_o')^{-1} = \frac{([H^{\oplus}] + K_a)k_{-2}}{k_2 k_4 K_a K_{NOBr} [ArNH_2]_T [H^{\oplus}]} + \frac{([H^{\oplus}] + K_a)}{k_2 K_a K_{NOBr} [ArNH_2]_T [H^{\oplus}][Br^{\ominus}]}$$

.....(3.6)

Hence a plot of $(k_o')^{-1}$ vs $[Br^-]^{-1}$ should yield a straight line, the slope of which will yield the value of k_2. The plots are shown in figs. 3.5 and 3.6 and the values of k_2 at 25°C obtained from these were 9.99×10^8 $dm^3 mol^{-1} s^{-1}$ and 4.77×10^7 $dm^3 mol^{-1} s^{-1}$ for sulphanilic acid and sulphanilamide respectively. The intercepts of the $(k_o')^{-1}$ vs $[Br^-]^{-1}$ plots yield values of the ratio k_{-2}/k_4 for each substrate and this provides a measure of the relative reactivity of bromide ion towards the nitrosammonium ion, $ArNH_2^+NO$[1]. The deduced ratio was 13 in each case and this will be discussed in more detail later.

Table 3.7 SULPHANILIC ACID BROMIDE RECIPROCAL DATA

$[Br^-]^{-1}/M^{-1}$	$10^2(k_o')^{-1}/s$
40.0	14.0
20.0	8.74
13.3	6.87
10.0	5.92

$(k_o^\circ = k_o = 5.30 \times 10^{-2}\ s^{-1})$

SLOPE = 2.67×10^{-3} mol dm^{-3} s

INTERCEPT = 3.34×10^{-2} s

Table 3.8 SULPHANILAMIDE BROMIDE RECIPROCAL DATA

$(Br^-)^{-1}/M^{-1}$	$10^2(k_o')^{-1}/s$
40.0	15.1
20.0	9.48
13.3	7.55
10.0	6.60

$(k_o' = k_o - 0.147)$

SLOPE = 2.83×10^{-3} mol dm^{-3} s

INTERCEPT = 3.75×10^{-2} s

As mentioned earlier the plots of k_o vs $[I^-]$ were linear indicating that $1 \gg K_{NOI}[H^+][I^-]$ throughout the range. Unfortunately the bimolecular rate constant for reaction of NOI with a substrate cannot be determined since knowledge of K_{NOI} is lacking. However, it is of interest to evaluate k_2K_{NOI} for each amine using equation 3.4. From the slopes of the k_o vs $[I^-]$ plots these values were determined as $k_2K_{NOI} = 8.51 \times 10^7$ $dm^9mol^{-3}s^{-1}$ for sulphanilic acid, and 3.53×10^6 $dm^9mol^{-3}s^{-1}$ for sulphanilamide, both at 25°C.

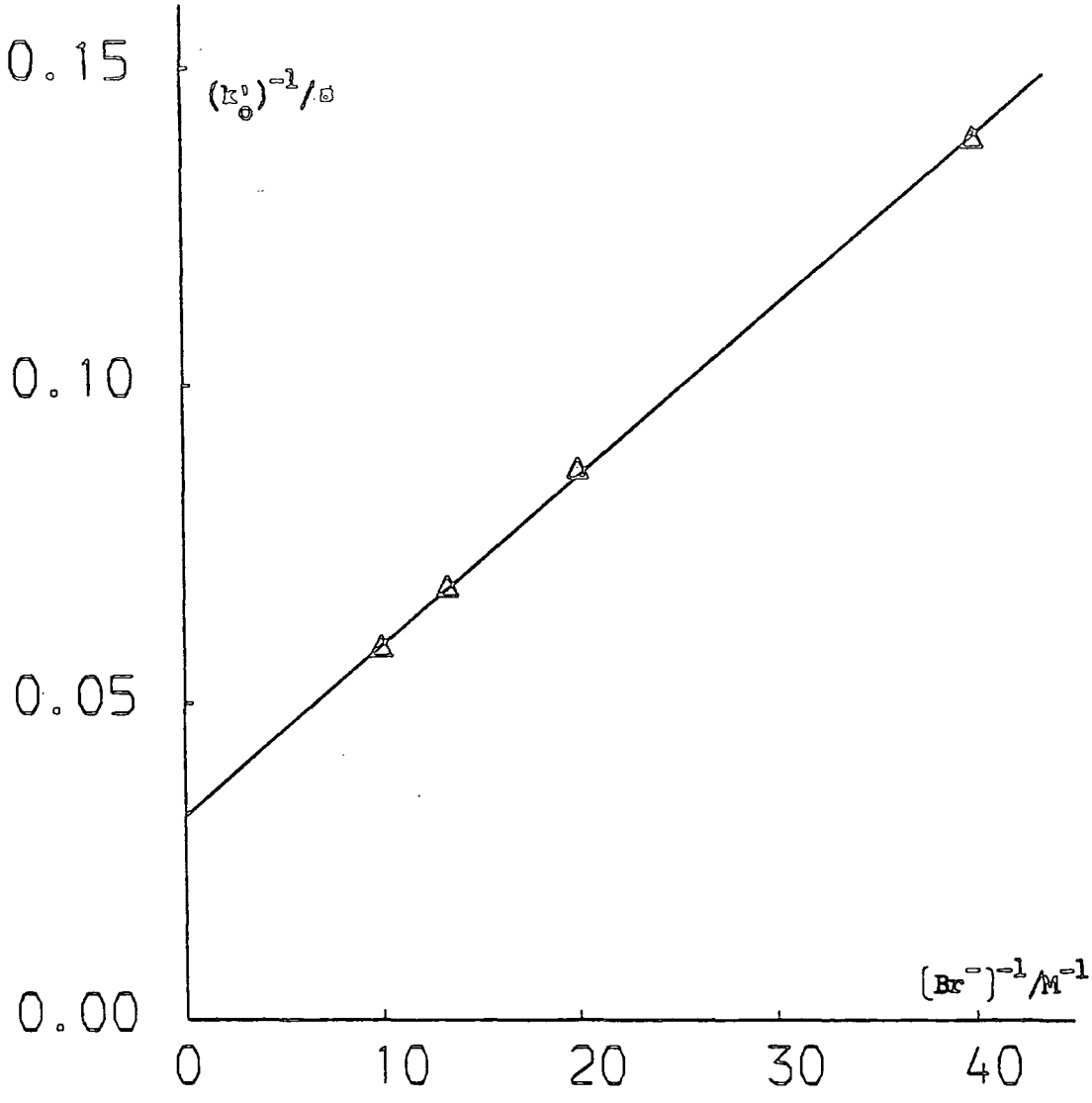


FIG. 3.5 — Sulphanilic Acid Bromide Reciprocal Data

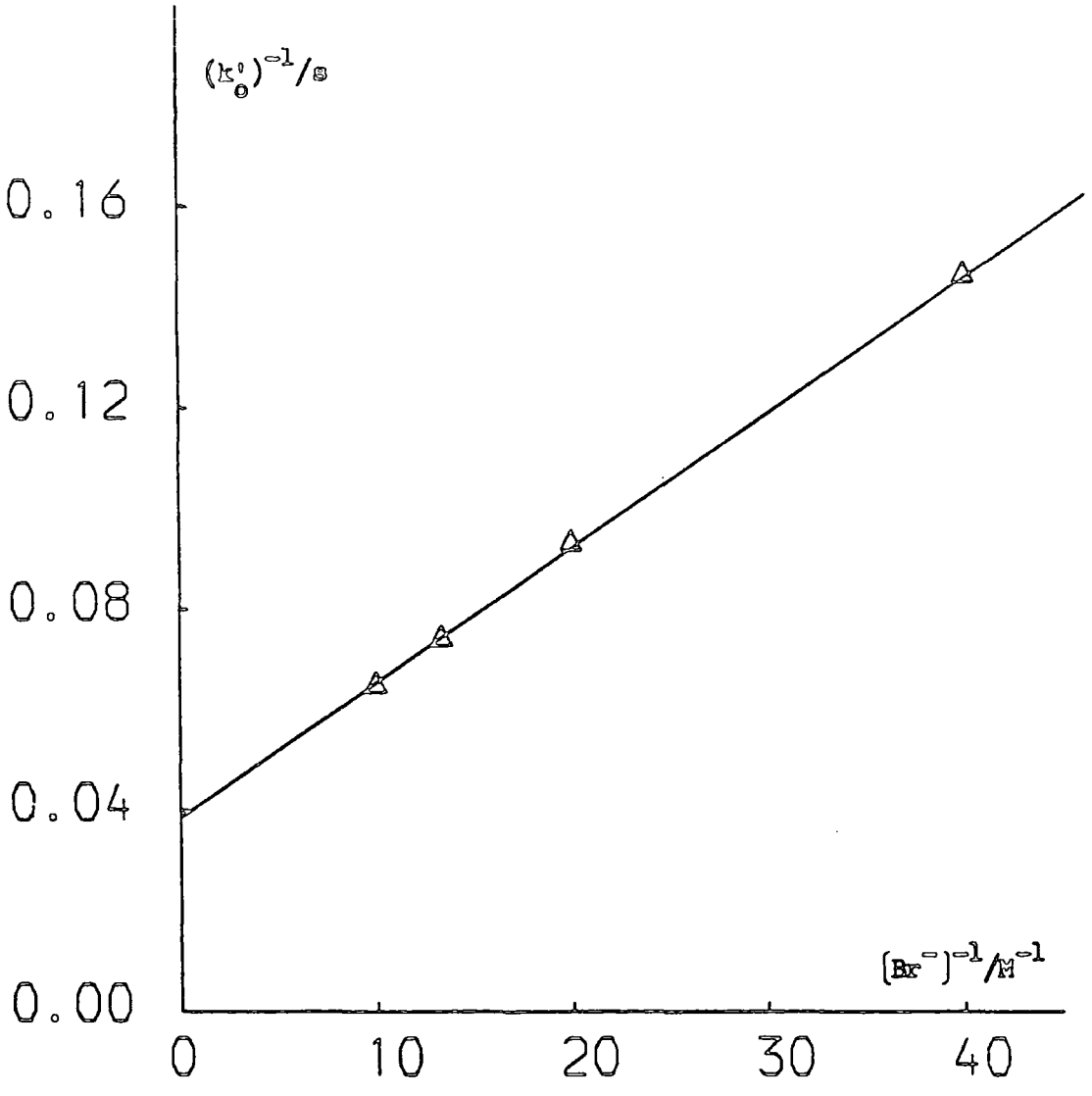


FIG. 3.6 — Sulphanilamide Bromide Reciprocal Data

3.4 Catalysis by Thiocyanate

Inspection of the data for the thiocyanate catalysed diazotisation of both substrates shows that the limiting condition $1 \gg K_{NOSCN}[SCN^-][H^+]$ applies throughout the range despite the fact that K_{NOX} is large relative to the halides ($K_{NOSCN} = 30$ dm^6mol^{-2} at 25°C)[5]. Hence the curvature of the k_o vs $[X^-]$ plots can again be attributed to the reversibility of the initial N-nitrosation step. The bimolecular rate constants k_2 for reaction of each amine can be obtained using equation 3.6 and the double reciprocal plots (figs. 3.7 & 3.8). These were 3.52×10^6 $dm^3mol^{-1}s^{-1}$ and 1.22×10^5 $dm^3mol^{-1}s^{-1}$ for sulphanilic acid and sulphanilamide respectively at 25°C, and the corresponding k_{-2}/k_4 ratios were 24 and 11. These latter values are compared with those for bromide below.

	k_{-2}/k_4	
Catalyst	Sulphanilic acid	Sulphanilamide
Br^-	13	13
SCN^-	24	11

In general k_{-2}/k_4 ratios increase as the electron withdrawing ability of ring substituents increases[1], suggesting that the major substituent effect here is in the denitrosation step (k_{-2}). Similar effects were found in the halide catalysed denitrosation of nitrosamines[6]. The fact that the step $k_{-2}[X^-]$ can compete with k_4, which involves proton tranfers and loss of a water molecule, may seem unlikely, but the evidence is quite clear from a variety of different experimental conditions[6].

and there seems to be no other plausible explanation.

Since k_4 is expected to be independent of the nucleophile these ratios give a direct comparison of the efficiences of the two anions in driving the nitrosation step in the reverse direction. The differences between the ratios for sulphanilamide are not significantly great but for sulphanilic acid the values show thiocyanate to be the stronger nucleophile.

Table 3.9 SULPHANILIC ACID THIOCYANATE CATALYSIS

$[ArNH_2] = 1.22 \times 10^{-2}M$ $[HNO_2] = 5.40 \times 10^{-5}M$ $[H^+] = 3.58 \times 10^{-2}M$

$10^3 \times [SCN^-]/M$	k_o/s^{-1}
1.74	1.29 ± 0.066
3.49	2.55 ± 0.045
6.97	4.65 ± 0.10
10.5	6.58 ± 0.11

(FIG. 3.1)

Table 3.10 SULPHANILIC ACID THIOCYANATE RECIPROCAL DATA

$[SCN^-]^{-1}/M^{-1}$	$(k_o')^{-1}/s$
574	0.809
287	0.400
143	0.218
95.6	0.153

$(k_o' = k_o - 5.30 \times 10^{-2})$

SLOPE = 1.29×10^{-2} mol dm^{-3} s

INTERCEPT = 3.03×10^{-2} s

Table 3.11 SULPHANILAMIDE THIOCYANATE CATALYSIS

$[ArNH_2] = 6.39 \times 10^{-3}$M $[HNO_2] = 5.40 \times 10^{-5}$M $[H^+] = 4.16 \times 10^{-2}$M

$10^3 \times [SCN^-]/M$	k_o/s^{-1}
1.74	1.05 ± 0.09
3.49	2.09 ± 0.05
6.97	3.70 ± 0.08
10.5	5.07 ± 0.10

(FIG. 3.3)

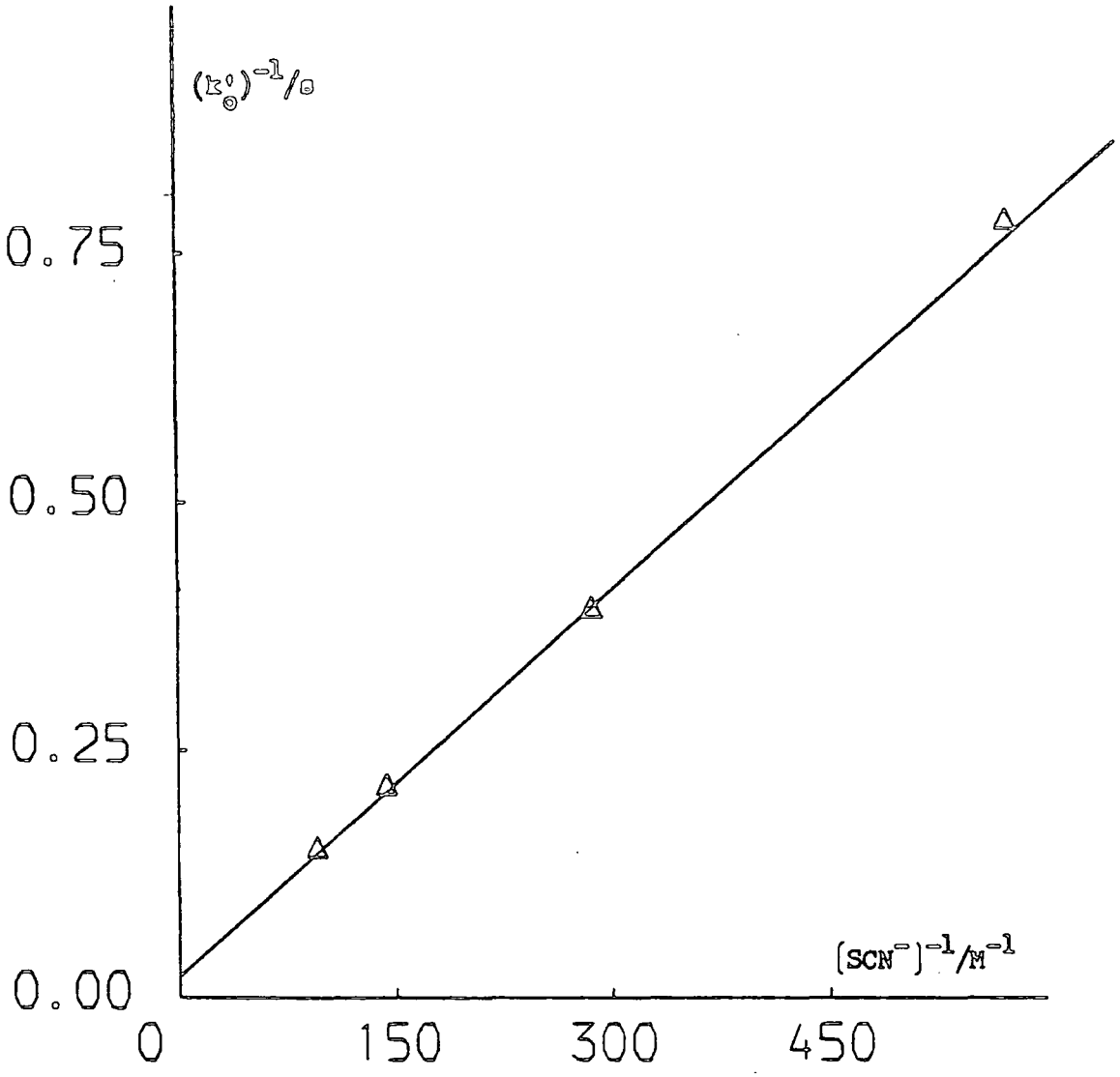


FIG. 3.7 — Sulphanilic Acid Thiocyanate Reciprocal Data

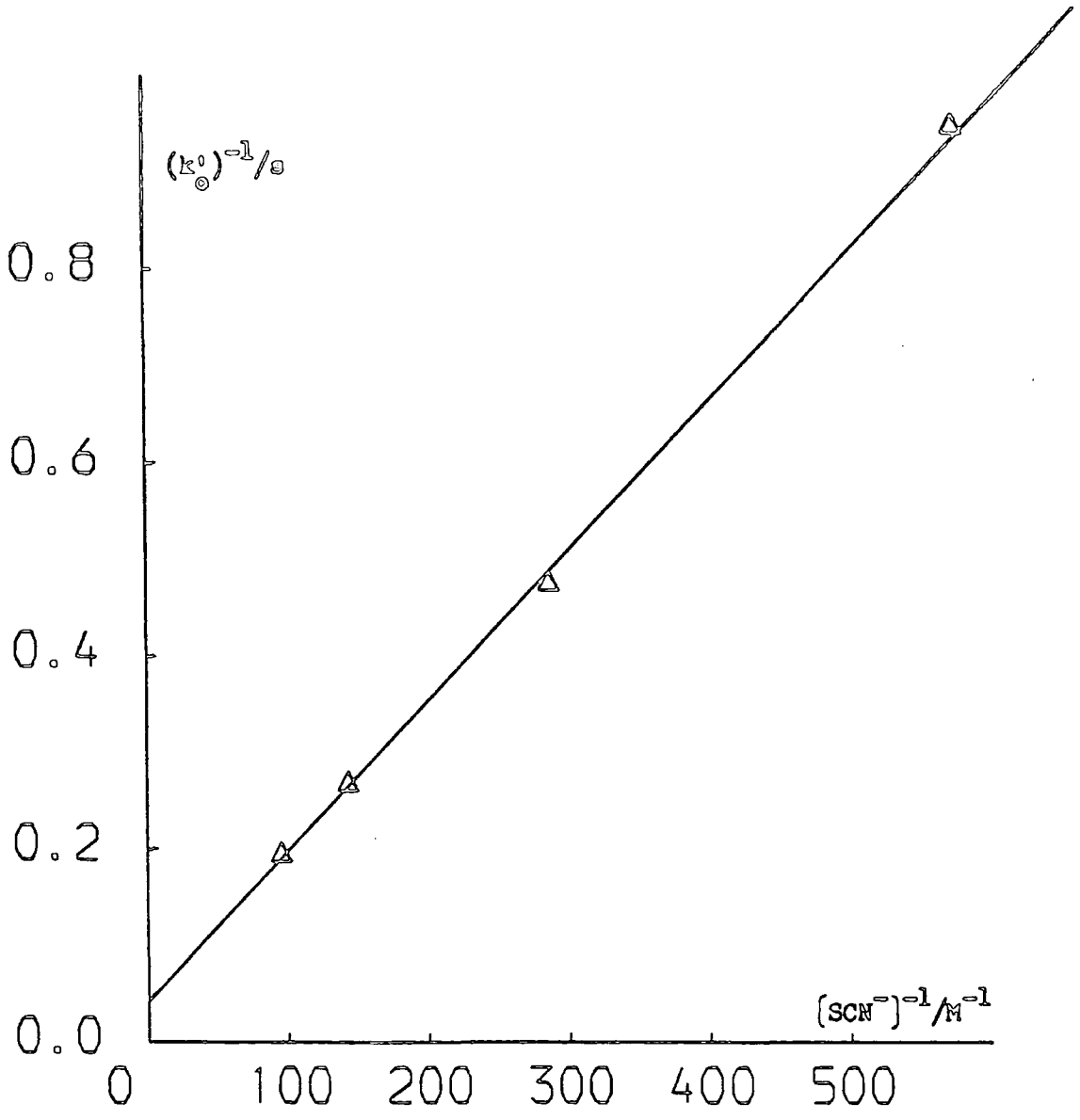


FIG. 3.8 — Sulphanilamide Thiocyanate Reciprocal Data

Table 3.12 SULPHANILAMIDE THIOCYANATE RECIPROCAL DATA

$[SCN^-]^{-1}/M^{-1}$	$(k_o')^{-1}/s$
574	1.09
287	0.509
143	0.281
95.6	0.202

$(k_o' = k_o - 0.147)$

SLOPE = 1.88×10^{-3} mol dm^{-3} s

INTERCEPT = 2.04×10^{-2} s

(see fig. 3.8)

3.5 Absence of Catalysis for 2,4-Dinitroaniline.

An attempt was made to study the diazotisation of 2,4-dinitroaniline catalysed by bromide and thiocyanate ion. However, in both cases a zero-order dependence on $[X^-]$ was observed, the values of k_o remaining constant (within experimental error) as the nucleophile concentration was varied. This behaviour can be explained with reference to scheme 3.2, which involves a reversible N-nitrosation step. The rate equation derived from this, by applying a steady-state approximation to $ArNH_2^{+}NO$, was:

$$k_o = \frac{k_2 k_4 K_a K_{NOX} [HNO_2]_T [X^-][H^+]}{k_{-2}[X^-] + k_4}$$

As in the previous chapter, solubility problems necessitated the use of a low amine concentration and an excess of nitrous acid to achieve first-order conditions, hence the use of $[HNO_2]_T$ instead of $[ArNH_2]_T$ in the above equation. In section 3.3 it was pointed out that if $k_{-2}[X^-]$ becomes comparable in magnitude to k_4 (as can occur at high $[X^-]$) the plot of k_o vs $[X^-]$ will level off. The complete lack of catalysis for 2,4-dinitroaniline can therefore be understood if the rate of the denitrosation step is much greater than the rate of decomposition of the intermediate nitrosammonium ion to form the product, i.e. if $k_{-2}[X^-] \gg k_4$ then the above equation reduces to:

$$k_o = \frac{k_2 k_4 K_a K_{NOX} [HNO_2]_T [H^+]}{k_{-2}} \quad (+ k_3 [HNO_2]_T [H^+])$$

and no catalysis by X^- is observed. This behaviour has been noted for many substrates containing electron withdrawing groups, such as sulphamic acid[7], urea[8], and amides in general[9]. The strong electron withdrawing properties of the two nitro substituents in the benzene ring reduce the electron density on the amino nitrogen which reduces the amine's reactivity towards NOX, and increases the reactivity of $ArNH_2^+NO$ towards X^-. Under the present conditions, therefore, the above equation is numerically equal to the average k_o value obtained for each nucleophile. However, no useful information can be obtained from this.

3.6 Catalysis by Thiourea

Catalysis by thiourea was observed for both sulphanilic acid and sulphanilamide and the treatment of the results is much the same as for the other nucleophiles already considered in this chapter.

Because of the large value of the equilibrium constant for formation of the nitrosothiouronium ion ($ONS\overset{+}{C}(NH_2)_2$, K_{NOX} = 5000 $dm^6 mol^{-2}$ at 25°C)[10] the total thiourea concentrations must be corrected because a fairly large proportion will be tied up as $ONS\overset{+}{C}(NH_2)_2$. This is done by calculating [NOX] as follows:

firstly $$[HNO_2]_T = [HNO_2]_F + [NOX]$$

and secondly $$[X^-]_T = [X^-]_F + [NOX]$$

also $$K_{NOX} = \frac{[NOX]}{[HNO_2]_F[X^-]_F[H^+]}$$

and by combining these expressions we obtain the following:

$$K_{NOX} = \frac{[NOX]}{[H^+]([HNO_2]_T - [NOX])([X^-]_T - [NOX])}$$

Rearrangement of this results in a quadratic equation which can be solved for [NOX]. Subtracting the values of [NOX] obtained in this way from the corresponding values of $[X^-]_T$ gives $[X^-]_F$ for each run. This was carried out for both substrates and the results are presented in the following tables.

Table 3.13 SULPHANILIC ACID THIOUREA CATALYSIS

$[ArNH_2] = 1.22 \times 10^{-2}M$ $[HNO_2] = 5.40 \times 10^{-5}M$ $[H^+]$ $3.58 \times 10^{-2}M$

$10^3 \times [SC(NH_2)_2]/M$	k_o/s^{-1}
0.971	0.290 ± 0.014
1.95	0.521 ± 0.023
2.92	0.735 ± 0.029
3.90	0.944 ± 0.037

(see fig. 3.2, page 64)

Table 3.14 SULPHANILAMIDE THIOUREA CATALYSIS

$[ArNH_2] = 6.39 \times 10^{-3}M$ $[HNO_2] = 5.40 \times 10^{-5}M$ $[H^+] = 4.16 \times 10^{-2}M$

$10^3 \times [SC(NH_2)_2]/M$	k_o/s^{-1}
0.970	0.263 ± 0.019
1.94	0.444 ± 0.031
2.92	0.552 ± 0.033
3.89	0.691 ± 0.035

(see fig. 3.4, page 66)

Close inspection of the plots shows that both exhibit very slight curvature. It is unlikely that this is due to the reversibility of the initial nitrosation step as was the case for bromide and thiocyanate. Rather, this curvature is attributed to the effect of K_{NOX} on the denominator of equation 3.3, which varies in magnitude from 1.2 to 1.7 over this range of $[SC(NH_2)_2]$. The curvature here is so slight, though, that it is possible to make an approximation and ignore the effect of $K_{NOX}[H^+][X^-]$ on 3.3. Thus we have:

$$k_o = \frac{k_2 K_a K_{NOX}[ArNH_2]_T[H^+][X^-]}{[H^+] + K_a}$$

as before. From the slopes of the two plots (213 $mol^{-1}s$ for sulphanilic acid and 127 $mol^{-1}s$ for sulphanilamide) the bimolecular rate constants for reaction of these substrates with the S-nitrosothiouronium ion were 6.03×10^3 $dm^3mol^{-1}s^{-1}$ and 1.96×10^2 $dm^3mol^{-1}s^{-1}$ for sulphanilic acid and sulphanilamide respectively at 25°C.

3.7 Summary

The results presented in this chapter show that for both sulphanilic acid and sulphanilamide marked catalysis by halide, thiocyanate, and thiourea occurs, whereas for 2,4-dinitroaniline no catalysis was observed due to the electron withdrawing effects of the two nitro groups. The bimolecular rate constants obtained from the data are presented in the table below together with some data for 4-nitroaniline taken from reference 1.

Bimolecular Rate Constants for $ArNH_2 + NOX \longrightarrow ArNH_2^{\oplus}NO + X^-$

	$k_2/dm^3 mol^{-1} s^{-1}$		
	Sulphanilic acid	Sulphanilamide	4-Nitroaniline[□□]
NOCl	1.44×10^9	1.96×10^8	2.10×10^8
NOBr	9.99×10^8	4.77×10^7	4.30×10^7
NOSCN	3.52×10^6	1.22×10^5	-
$ONS\overset{\oplus}{C}(NH_2)_2$	6.03×10^3	1.96×10^2	-
NOI[□]	(8.51×10^7)	(3.53×10^6)	-

□ values reported for NOI are k_2K_{NOI} values □□ taken from ref. 1

Two notable trends are evident in this table. Firstly, there is the marked decrease in the values of the rate constants down each column, due to the differences in the reactivities of the various NOX species towards the substrate. The following reactivity trend is now well established, having been observed for many substrates[6].

$$NOCl > NOBr > NOSCN > ONS\overset{\oplus}{C}(NH_2)_2$$

However, the overall rate of the reaction is governed more by the magnitude of the constant K_{NOX} than the rate of reaction of NOX with the substrate[6]. NOI is omitted from the discussion since values of k_2 for reaction of NOI cannot be determined, as mentioned earlier,

although it has been suggested that NOI is about as reactive as nitrosyl thiocyanate[6].

Secondly, the k_2 values for sulphanilamide are consistently less than the corresponding values for sulphanilic acid. This is a consequence of the greater basic strength of sulphanilic acid, making it more nucleophilic and hence more susceptible to attack by NOX than sulphanilamide. It is also interesting to note the difference in behaviour between 4-nitroaniline and 2,4-dinitroaniline, where the introduction of a second nitro group is sufficient to remove catalysis completely.

The k_2 values reported in the table above fit reasonably well onto the log k_2 vs pK_a plot, illustrating that the susceptibilities of aniline derivatives to electrophilic nitrosation by a variety of reagents follows the same trend as their basicities.

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3.8 REFERENCES - Chapter 3

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CHAPTER 4

DIAZOTISATION of HETEROAROMATIC AMINES

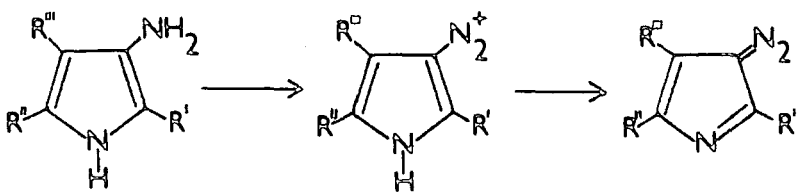
4.1 Introduction

Despite the large volume of kinetic data available in the literature on the formation of diazonium ions from aniline derivatives, relatively few studies have been made on the diazotisation of heteroaromatic amines which are of increasing commercial importance in the manufacture of azo dyes. In the important monograph by Zollinger[1] published in 1961 they are only briefly mentioned, and it was pointed out that due to the poor stability of heterocyclic diazonium salts the desired azo dyes are prepared by oxidative coupling of the corresponding hydrazones. The situation has changed drastically since then and nowadays dyes with heterocyclic diazo components are prepared on a large scale and are very important because of their excellent brightness and higher intensity absorption bands[2], as borne out by the amount of patent literature on the subject[3]. Heterocyclic diazonium salts are also interesting as synthetic intermediates for the preparation of compounds of potential pharmaceutical value[4]. Of the studies that have been made, perhaps the most important is that of Kalatzis[5] who studied the kinetics of diazotisation of aminopyridines in dilute acid solutions.

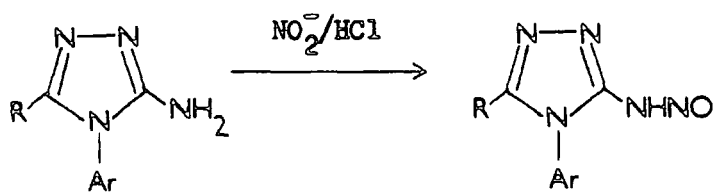
In general, the diazotisation of heteroaromatic amines is considered to involve the same steps as for aniline derivatives[6] (scheme 1.1) except, in some cases, for an additional step after formation of the diazonium ion:

$$HAr\text{-}N_2^+ \rightleftharpoons \bar{A}r\text{-}N_2^+ \longleftrightarrow Ar\text{=}N_2 \qquad (I)$$

(here the symbol Ar represents a heteroaromatic ring minus two hydrogen atoms). The products (I) are diazo compounds which are generally more stable than the other species. Such diazo compounds arise when a base is added to the diazonium solution or when the aromatic ring possesses a hydrogen atom acidic enough to be donated to the medium[7]. An example of this is found in the diazotisation of substituted aminopyrroles[8]:

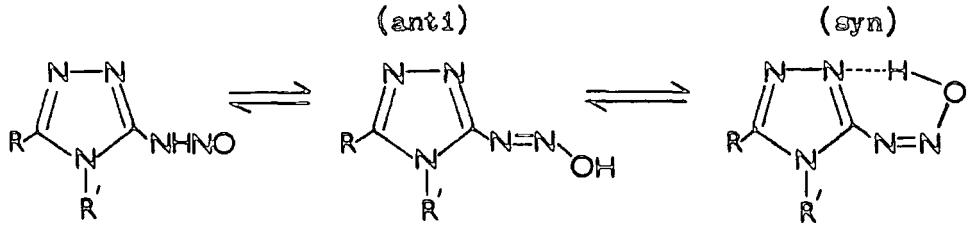


In some cases reaction with sodium nitrite in acid solution leads to the formation of a stable primary nitrosamine rather than a diazonium ion[4]. This was noted by Gehlen[9] who isolated a primary nitrosamine after reaction of a 4-N-substituted aminotriazole in 18% hydrochloric acid solution:



The acid concentration here is critical since at lower acidities the corresponding triazene (RAr-N=N-NH-ArR) is formed, and at higher acidities chlorodediazoniation occurs. This phenomenon is a feature of the diazotisation of many amines of the higher azoles and provides

direct evidence for the intermediacy of primary nitrosamines in the diazotisation process[4]. The stability of these primary nitrosamines is attributed to nitrosamine-diazohydroxide tautomerism and stabilisation through hydrogen bonding:



A labile proton in the molecule will be involved in tautomeric equilibria itself which will disrupt this stabilisation, thereby allowing diazonium ion formation to occur. Diazonium salts derived from heteroaromatic amines undergo the usual dediazoniation and azo-coupling reactions of benzenoid aromatics as described in section 1.8.

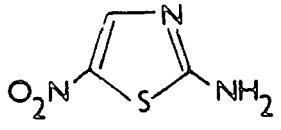
Thus, in the case of heteroaromatic amines several products are formed, depending upon the structure of the heterocycle. If an acidic proton is present diazotisation leads to a diazonium salt and a diazo compound, whereas in the absence of such a proton a primary nitrosamine may be formed which takes part in a tautomeric equilibrium with a diazohydroxide stabilised by hydrogen bonding. A certain amount of diazonium salt is also present, its concentration increasing with the acidity of the medium. Diazotisation of 6-membered heterocycles results in the formation of diazonium salts or their dediazoniation products[4]. Primary nitrosamines have not been isolated or directly detected for these systems and the same variety of products as found with the five-membered ring compounds is not encountered[4].

4.2 Scope of the Present Work

It is of interest to establish whether the same catalytic influences (of halide ion, thiocyanate ion, etc.) as occur in the benzenoid aromatic systems are operational for the heteroaromatic amines and to correlate these reactivities with the structures of the amines. The results presented in this chapter describe the effects of acid, bromide ion, and thiocyanate ion on the rate of diazotisation of 2-amino-5-nitrothiazole and 3-amino-1,2,4-triazole.

4.3 2-Amino-5-nitrothiazole

Sulphur azoles such as aminothiazoles and aminoisothiazoles are readily diazotised in strong oxyacids to form the corresponding diazonium salts which may be isolated[10]. 2-Amino-5-nitrothiazole (I, below) forms a highly reactive diazonium salt and many examples of its use in the manufacture of azo dyes can be found in the literature[11,12].



(I)

Angyal and Angyal[13] suggested that the diazotisation of primary N-heteroaromatic amines involves the non-protonated species' which, because of deactivation of the amino group by the ring nitrogen, react only in concentrated acid solution with the strongly electrophilic nitrosonium ion. They also suggested that the stabilising resonance of the type found in the benzenoid aromatic systems

(chapter 1, p.22) does not exist between the N-heteroaromatic ring and the diazonium group. The suggested absence of aromatic character from these diazonium ions was considered responsible for their instability which was compared with that of the aliphatic diazonium ions. Kalatzis[14] has pointed out, however, that diazotisation does occur in dilute acid solutions in which the concentration of NO^+ is very low. In fact, Kalatzis studied the diazotisation of 4-aminopyridines and showed that the reaction involved the endocyclic-N-protonated amine. Also, the argument against stabilising resonance is not justified since heteroaromatic diazonium salts can be isolated and coupled with alkaline β-naphthol[5].

In aminothiazoles there are two possible protonation sites - the exocyclic (amino) nitrogen atom and the endocyclic (imino) nitrogen. It has been shown that substituent effects in 5-substituted-2-aminothiazoles are satisfactorily expressed by the σ_{meta} values of the substituents[15]. However, the use of σ_{para} does not give acceptable correlations with experimentally determined pK_a values for 2-aminothiazoles and 2-N,N-dimethylaminothiazoles substituted in position 5, and this strongly supports the conclusion that the endocyclic nitrogen atom is the more basic of the two[16]. The pK_a values of 2-aminothiazole itself have been measured[17] as 5.28 for the endocyclic nitrogen atom and -3.22 for the amino group.

The amine under consideration here, namely 2-amino-5-nitrothiazole, is only slightly soluble in water and so, as for the nitroanilines, reactions were carried out with nitrous acid in excess. It was necessary to follow the decrease in intensity of the long-

wavelength side of the absorption band centered at 382nm because the absorptions due to nitrous acid interfered at shorter wavelengths. The presence of the diazonium ion in the reaction solution was demonstrated by coupling with N,N-dimethylaniline, as described in ch.6, page 169. The order with respect to nitrous acid was unity, as shown by the data in the following table.

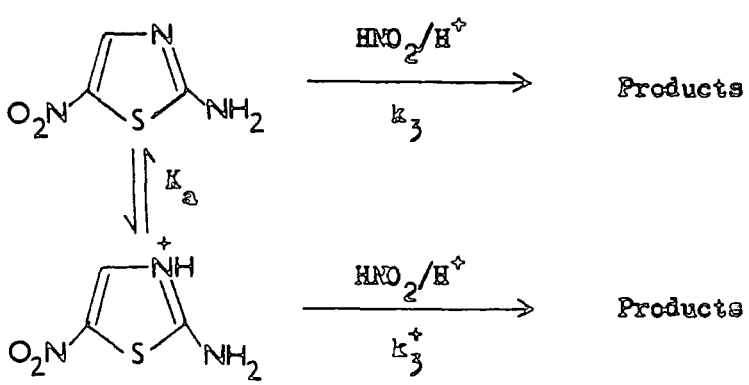
Table 4.1 Nitrous Acid Dependence

[Amine] = 5.10×10^{-5}M λ = 405nm

$10^2[HNO_2]$/M	$10^2[H^+]$/M	$10^3 k_\psi / s^{-1}$
1.17	4.83	1.72 ± 0.075
2.33	4.87	3.40 ± 0.15
4.67	4.83	6.71 ± 0.27

4.3.1 Acid Catalysis

As mentioned earlier, N-heteroaromatic amines can, in principle, undergo diazotisation via either the protonated or non-protonated forms. Therefore, the reaction scheme for this amine is as follows:



The superscript "+" on the rate constant k_3^+ is used here to distinguish rate constants for reaction of positive species' in the following rate equations. The rate equation is thus:

$$\text{RATE} = k_3[A][HNO_2]_T[H^+] + k_3^+[HA^+][HNO_2]_T[H^+]$$

where A and HA^+ are the neutral and protonated amines respectively. Application of the protonation equilibrium for HA^+ gives:

$$\text{RATE} = \frac{k_3K_a[A]_T[HNO_2]_T[H^+]}{[H^+] + K_a} + \frac{k_3^+[A]_T[HNO_2]_T[H^+]^2}{[H^+] + K_a}$$

and so
$$k_o = \frac{k_3K_a[HNO_2]_T[H^+]}{[H^+] + K_a} + \frac{k_3^+[HNO_2]_T[H^+]^2}{[H^+] + K_a} \qquad (4.1)$$

and, as for the aniline derivatives, two limiting forms are possible: when $K_a >> [H^+]$ we have

$$k_o = k_3[HNO_2]_T[H^+] + \frac{k_3^+}{K_a}[HNO_2]_T[H^+]^2 \qquad (4.2)$$

and when $K_a << [H^+]$ we have

$$k_o = k_3K_a[HNO_2]_T + k_3^+[HNO_2]_T[H^+] \qquad (4.3)$$

The data obtained in the study of the acid catalysed diazotisation of this amine are presented in the table below.

Table 4.2 2-Amino-5-nitrothiazole - Acid Catalysis

$[Amine] = 1.56 \times 10^{-4}M$ $[HNO_2]_T = 2.14 \times 10^{-2}M$ $\lambda = 405nm$

$[H^+]/M$	$10^3 k_o/s^{-1}$
0.0941	3.83 ± 0.15
0.119	4.61 ± 0.04
0.141	5.95 ± 0.13
0.189	7.25 ± 0.16
0.210	8.47 ± 0.15

SLOPE = 0.0390 $mol^{-1}dm^3s^{-1}$

INT. = 1.61×10^{-4} s^{-1}

(FIG. 4.1)

From the above equations it can be seen that when $K_a \simeq [H^+]$ one could expect a plot of k_o vs $[H^+]$ to be curved, convex to the k_o axis and becoming linear as $[H^+] \gg K_a$ is approached. Using the reported K_a value[15] of 0.25M (endocyclic protonation) for this amine the plot should exhibit pronounced curvature up to about 3M H^+ (assuming compensation for medium effects and the application of a suitable acidity function). No curvature was observed over the acid range 0.05-0.5M and this would seem to indicate that the reaction involves only the neutral thiazole molecule, since this would require the condition $K_a \gg [H^+]$ to be satisfied. A linear dependence would also

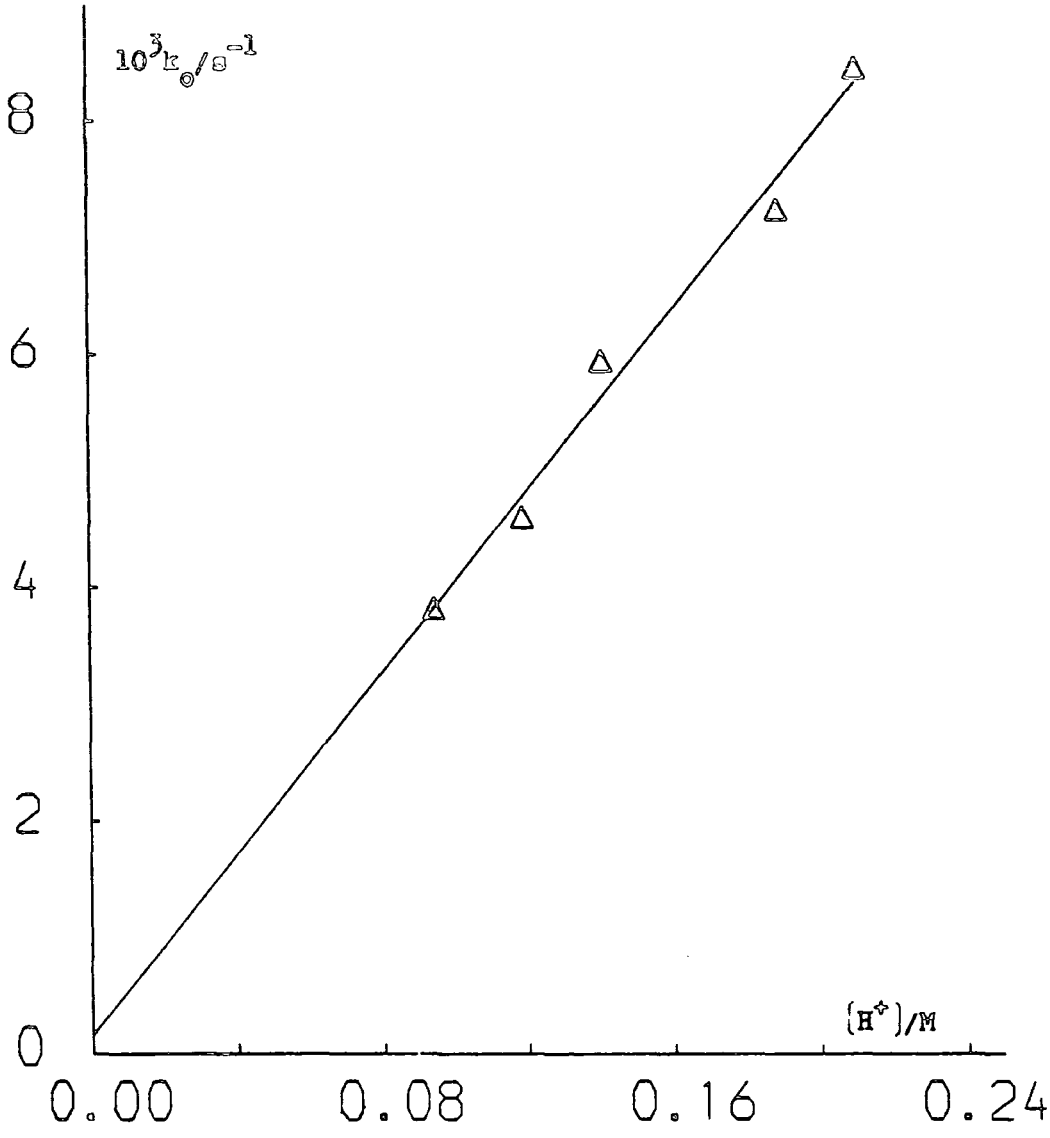


FIG. 4.1 — Acid Catalysed Diazotisation of 2-Amino-5-nitrothiazole

result if $K_a \ll [H^+]$ but in this case a non-zero intercept would be observed (see eqn. 4.3). Inspection of fig. 4.1 shows that the intercept is zero (within experimental error). So, there are two possible explanations for the shape of fig. 4.1. Firstly, it may be that the reported K_a value of 0.25M is in error. Assuming that the K_a value is actually much larger than this one could expect the observed linear dependence as $K_a \gg [H^+]$ applies. The possibility that $K_a \ll [H^+]$ is ruled out by the zero intercept of the plot. Secondly, if the K_a value is correct then the data may not be reliable since $K_a \simeq [H^+]$ predicts curvature. Neither of these two explanations is satisfactory, particularly the former. In another report[18] the K_a value for this amine is given as 0.12M and because of the reasonable agreement between this and the value of 0.25M it is not considered wise to refute both in order to explain the trend shown by the few scattered data presented here. For this reason a full discussion of acid catalysis will be left until the end of this section where a second study of the kinetics is reported.

4.3.2 Catalysis by Bromide

As is the case for many amines, the diazotisation of 2-amino-5-nitrothiazole was found to be catalysed by added bromide ion, presumably via the intermediacy of NOBr. The k_o values obtained in the study are laid out in the table below. The plot of k_o vs $[Br^-]$ is linear with a non-zero intercept, as shown in fig. 4.2.

Since the K_a value of this amine is relatively small (reported[18,15] as 0.12M and 0.25M) it is expected that the electron-withdrawing effects of the protonated endocyclic nitrogen atom would reduce the

Table 4.3 2-Amino-5-nitrothiazole - Bromide Catalysis

$[Amine] = 5.07 \times 10^{-5}M$ $[H^+] = 4.41 \times 10^{-2}M$ $[HNO_2] = 5.22 \times 10^{-2}M$

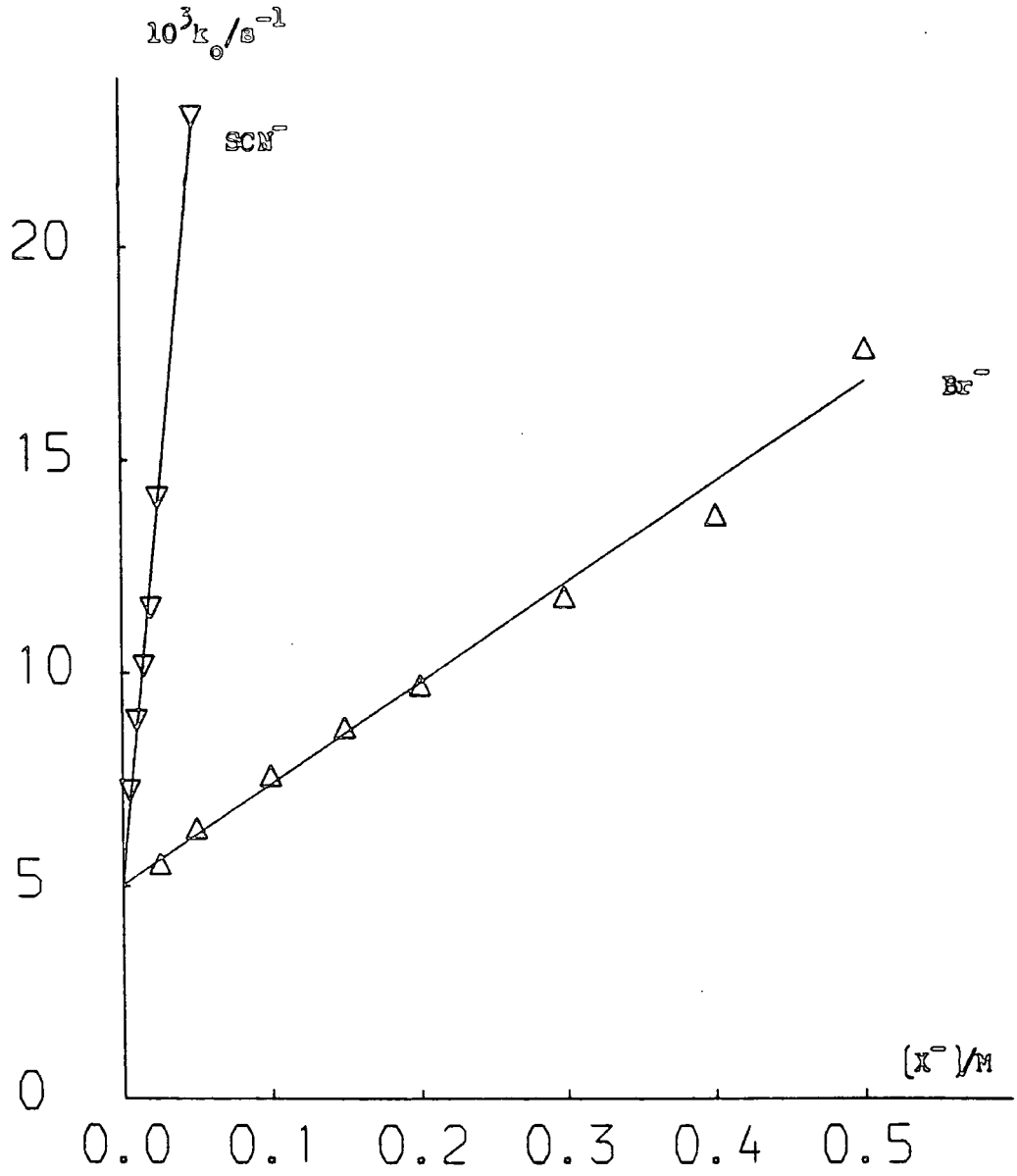
$[Br^-]/M$	$10^3 k_o/s^{-1}$
0.0251	5.52 ± 0.08
0.0501	6.37 ± 0.11
0.100	7.60 ± 0.06
0.150	8.72 ± 0.35
0.200	9.71 ± 0.19
0.300	11.8 ± 0.50
0.402	13.7 ± 0.26
0.502	17.7 ± 0.17

SLOPE = 0.0237 $mol^{-1}dm^3s^{-1}$

INT. = 5.02×10^{-3} s^{-1}

(FIG. 4.2)

'availability' of the lone pair of electrons on the exocyclic nitrogen even further, thus reducing the molecule's affinity for NOX. Also, as was mentioned earlier, the pK_a value of the exocyclic nitrogen atom in the parent molecule (2-aminothiazole) is -3.22 (ref. 17) and the introduction of a 5-nitro substituent will reduce this even further. In any case the acid concentration used in this study (0.04M) is not

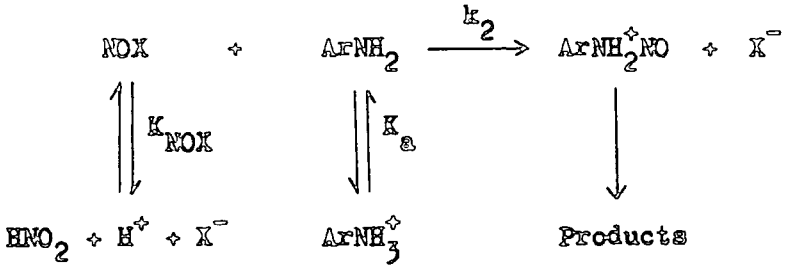


▽ Thiocyanate

△ Bromide

FIG. 4.2 — Nucleophile Catalysed Diazotisation of 2-Amino-5-nitrothiazole

sufficiently large for appreciable protonation to occur at either site and so the rate constant k_2 for reaction of the amine with NOX can be evaluated by assuming that reaction occurs via the neutral thiazole molecule only. Thus we have:



Since this is the same as scheme 3.1 (page 56) the same rate equation (3.3, p.58) applies, substituting $[HNO_2]_T$ for $[ArNH_2]_T$ since in the present study nitrous acid is in excess. From the plot, then, we have:

$$\text{Slope} = k_2[HNO_2]_T[H^+]K_{NOBr} = 0.0237 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1}$$

$$\text{and so } k_2 = 202 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1} \quad \text{at } 25^\circ\text{C}$$

The intercept of the k_o vs $[Br^-]$ plot is given by:

$$\text{Int.} = k_3[HNO_2]_T[H^+] = 5.02 \times 10^{-3} \text{ s}^{-1}$$

which gives a value of $2.18 \text{ mol}^{-2}\text{dm}^6\text{s}^{-1}$ for k_3 at 25°C.

4.3.3 Catalysis by Thiocyanate

As for bromide, thiocyanate catalysis was observed in the diazotisation of this amine. The data are presented in the table below.

Table 4.4 2-Amino-5-nitrothiazole - Thiocyanate Catalysis

$[\text{Amine}] = 5.07 \times 10^{-5}\text{M}$ $[H^+] = 4.42 \times 10^{-2}\text{M}$ $[HNO_2] = 5.20 \times 10^{-2}\text{M}$

$10x[SCN^-]/\text{M}$	$10^3 k_o/s^{-1}$
0.0502	7.24 ± 0.04
0.100	8.88 ± 0.11
0.151	10.2 ± 0.14
0.201	11.5 ± 0.14
0.249	14.1 ± 0.50
0.497	23.1 ± 0.84

SLOPE = 0.358 $mol^{-1}dm^3s^{-1}$

INT. = $5.05 \times 10^{-3} s^{-1}$

(FIG. 4.2)

And, as before, a linear plot was obtained. Therefore,

$$\text{Slope} = k_2[HNO_2]_T[H^+]K_{NOSCN} = 0.358\ mol^{-1}dm^3s^{-1}$$

and so

$$k_2 = 5.19 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1} \text{ at } 25^\circ\text{C}$$

As for bromide, the intercept of the k_o vs $[SCN^-]$ plot yields a value of 2.20 $\text{mol}^{-2}\text{dm}^6\text{s}^{-1}$ for k_3, in excellent agreement with the value obtained previously.

Thus, as for the aniline derivatives, the trend in the reactivities of these NOX species is the same, i.e. NOBr > NOSCN, as shown by the bimolecular rate constants of 202 $\text{mol}^{-1}\text{dm}^3\text{s}^{-1}$ and 5.19 $\text{mol}^{-1}\text{dm}^3\text{s}^{-1}$ for each species respectively. Also, the general catalytic trend SCN^- > Br^- is observed in the reaction of the thiazole, as was the case for the aniline derivatives studied in chapter 3, and for many other substrates[19]

4.3.4 Acid Catalysis in the Presence of Nucleophiles

Since it was expected that this amine would undergo diazotisation via both the protonated and non-protonated forms, a study of the acid catalysed reaction was undertaken in which there was a constant concentration of added nucleophile. This would enable the evaluation of the rate constants k_2 for reaction with NOBr and NOSCN from a rather complex rate equation derived from a scheme involving both neutral and protonated forms of the substrate (see section 4.4.2). However, later consideration of the K_a value for this amine suggested that in this case reaction would probably occur via the non-protonated amine only. Thus it was possible to evaluate k_2 for reaction of NOBr and NOSCN without recourse to this acid dependence in the presence of X^-.

However, since there is uncertainty over the validity of the acid data presented in section 4.3.1 the data presented here conveniently provide a means of checking on the pK_a value of the amine.

For acid catalysis in the presence of X^- (assuming no reaction of the protonated amine) we have:

$$k_o = \frac{k_3 K_a (HNO_2)_T (H^+)}{(H^+) + K_a} + \frac{k_2 (HNO_2)_T (H^+)(X^-) K_a K_{NOX}}{(H^+) + K_a}$$

$$\text{i.e.} \quad k_o = (k_3 + k_2 (X^-) K_{NOX}) \frac{K_a (HNO_2)_T (H^+)}{(H^+) + K_a} \qquad (4.4)$$

As before, if $(H^+) \simeq K_a$ then the above equation predicts curvature of the plot of k_o vs (H^+). The data for acid dependence in the presence of Br^- and SCN^- are presented below and shown graphically in fig. 4.3.

In both cases plots of k_o vs (H^+) were curved. If we now take the reciprocal form of equation 4.4 we have:

$$k_o^{-1} = \frac{1}{(k_3 + k_2 (X^-) K_{NOX})(HNO_2)_T (H^+)} + \frac{1}{(k_3 + k_2 (X^-) K_{NOX})(HNO_2) K_a}$$

.....(4.5)

and so plots of k_o^{-1} vs $(H^+)^{-1}$ should result in straight lines, the intercepts of which will yield the value of the constant K_a. The recip-

rocal data are presented in tables 4.7 and 4.8 and shown graphically in fig. 4.4.

Table 4.5 Acid Dependence at $[Br^-] = 0.997M$

$[Amine] = 1.76 \times 10^{-4}M$ $[HNO_2] = 0.020M$

$10 \times [H^+]/M$	$10^3 k_o/s^{-1}$
0.263	11.0 ± 0.53
0.738	22.0 ± 1.3
1.19	27.4 ± 1.5
1.67	29.0 ± 1.7
2.11	28.9 ± 1.3
3.25	27.8 ± 1.8

(FIG. 4.3)

Table 4.6 Acid Dependence at $[SCN^-]$ = 0.0255M

$[Amine] = 1.54 \times 10^{-4}M$ $[HNO_2] = 0.0203M$

$10 \times [H^+]/M$	$10^3 k_o/s^{-1}$
0.214	3.03 ± 0.18
0.446	5.38 ± 0.24
0.912	8.79 ± 0.37
1.35	11.9 ± 0.63
1.82	12.5 ± 0.59
2.30	13.4 ± 0.65

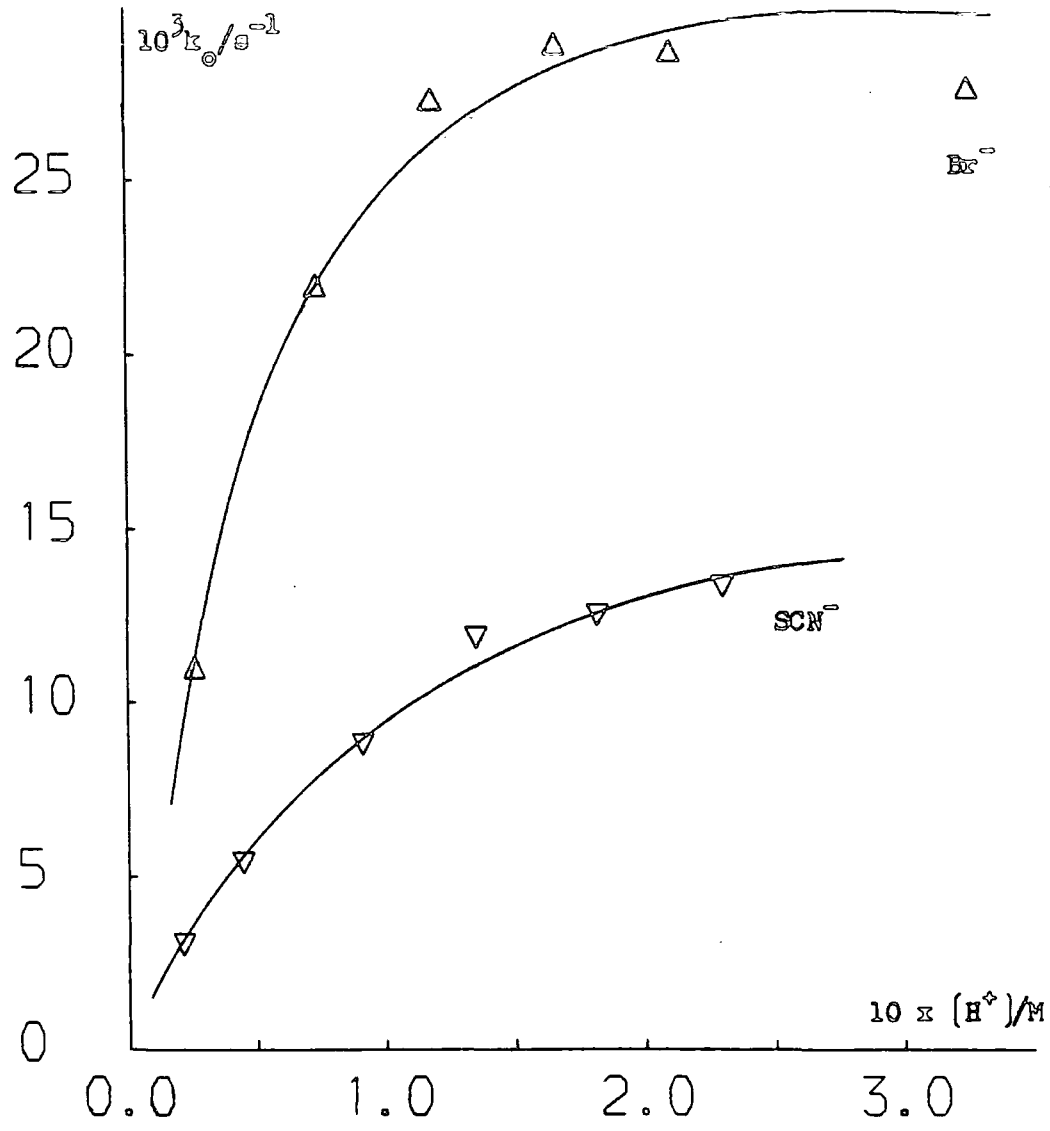
(FIG. 4.3)

Table 4.7 H^+/Br^- Reciprocal Data

$[H^+]^{-1}/M^{-1}$	k_o^{-1}/s
38.0	90.6
13.6	45.4
8.42	36.5
5.99	34.5

SLOPE = 1.79 mol dm^{-3} s

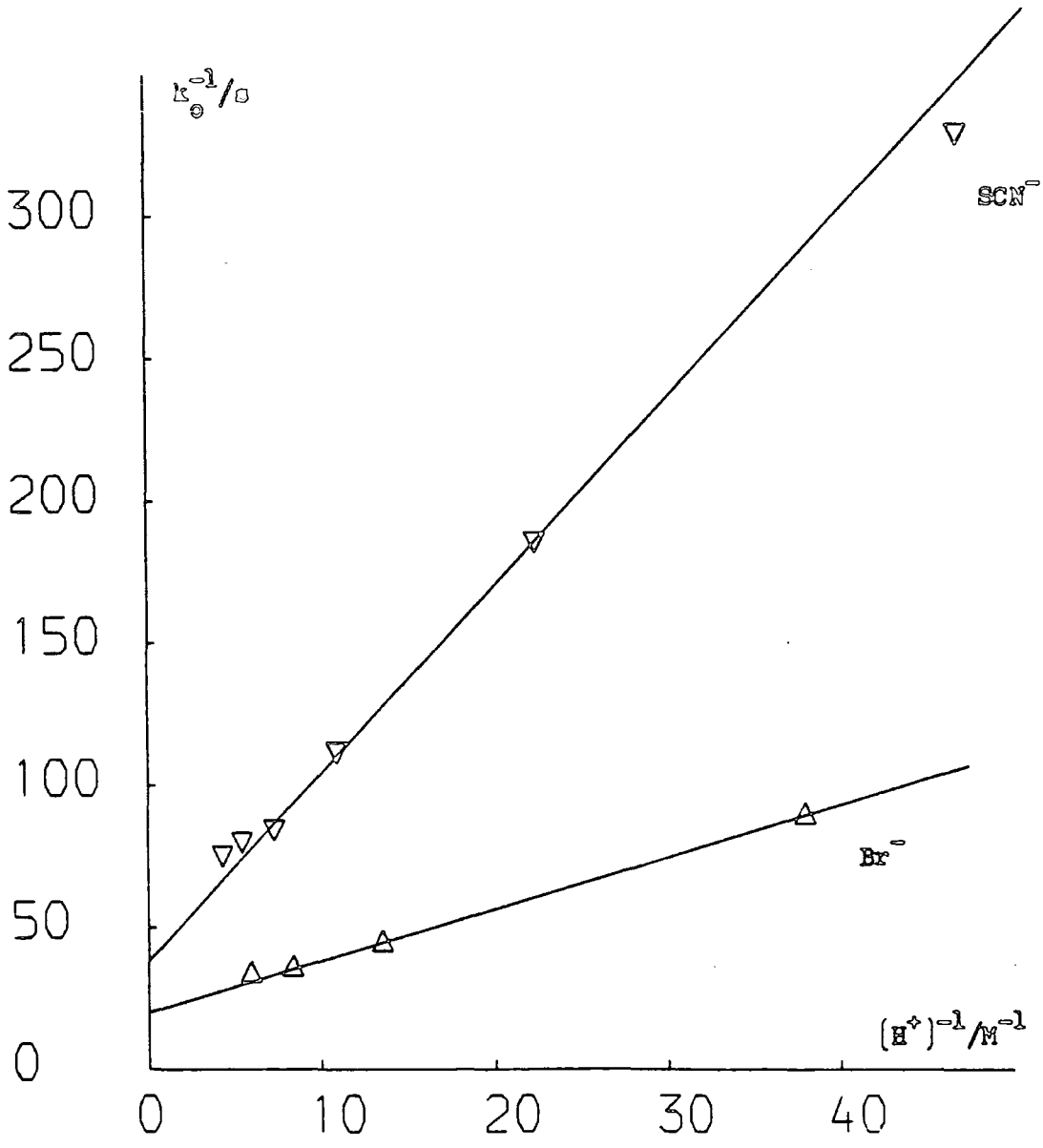
INT. = 22.2 s



▽ Thiocyanate

△ Bromide

FIG. 4.3 — Acid Dependence in the Presence of constant [Nucleophile] for 2-Amino-5-nitrothiazole.



▽ Thiocyanate

△ Bromide

FIG. 4.4 — H^+/X^- Reciprocal Plot for 2-Amino-5-nitrothiazole

Table 4.8 H^+/SCN^- Reciprocal Data

$[H^+]^{-1}/M^{-1}$	k_o^{-1}/s
46.8	330
22.4	186
11.0	111
7.39	84.2
5.49	79.8
4.35	74.9

SLOPE = 6.09 mol $dm^{-3}s$

INT. = 45.3 s

(FIG. 4.4)

From equation 4.5 we have:

$$INT. = ((k_3 + k_2[X^-]K_{NOX})[HNO_2]_T K_a)^{-1}$$

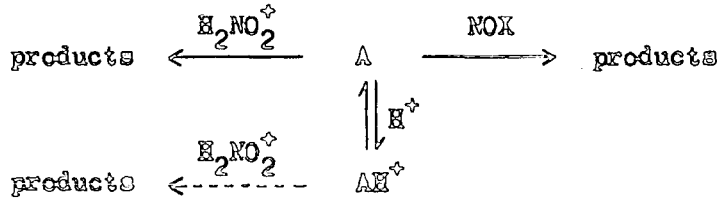
Using the value of 2.19 $mol^{-2}dm^6s^{-1}$ for k_3 obtained in sections 4.3.2 and 4.3.3 we have K_a = 0.174M (from H^+/Br^-) and K_a = 0.176M (from H^+/SCN^-) which are in good agreement with the literature values of 0.12M[18] and 0.25M[15]

4.3.5 Summary

The study of the nucleophile catalysed diazotisation of the thiazole has yielded bimolecular rate constants for reaction of this amine with NOX (X = Br, SCN) which follow the same trend as has been observed consistently in studies of the nucleophile catalysed reactions of the aniline derivatives reported in this work and in many others[19]

i.e.	Reactivity :	NOBr > NOSCN
	Catalytic Efficiency :	Br^- < SCN^-

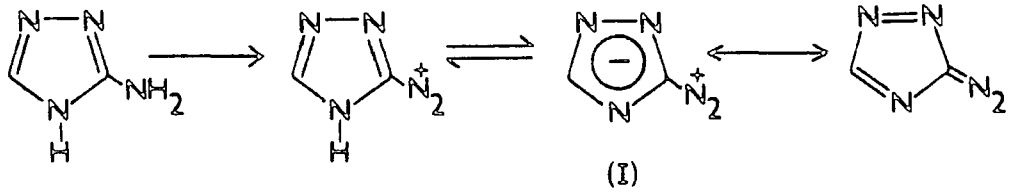
The data obtained for acid catalysis reported in section 4.3.1 would seem to be unreliable since they fit neither the scheme involving both the protonated and non-protonated substrate, nor that involving the non-protonated amine alone. This is supported by the fact that variation of $[H^+]$ in the presence of X^- yielded curved plots of k_o vs $[H^+]$ in both cases (X^- = Br^-, SCN^-), as predicted by equation 4.1 when $K_a \simeq [H^+]$, whereas by varying $[H^+]$ with no nucleophile present a linear plot of k_o vs $[H^+]$ was obtained (albeit with fairly scattered data). These H^+/X^- data yielded K_a values of 0.174M and 0.176M, agreeing very well with each other and the literature values of 0.12M and 0.25M. The value for k_3 of 2.19 $mol^{-2}dm^6s^{-1}$ was obtained using the Br^- and SCN^- catalysis data, both sets of data yielding the same value adding yet more weight to the argument against the validity of the original acid data. It would seem, then, that reaction occurs via the non-protonated amine only, with perhaps a very small component due to the protonated form for acid catalysis. The reaction scheme is as follows:



As mentioned earlier in this chapter, diazotisation of heterocyclic amines with no labile hydrogen atom can yield stable primary nitrosamines[4]. Some circumstantial evidence in support of this was obtained - a bright yellow colour, typical of nitrosamines, was observed initially when the reaction mixture was mixed with a buffered (pH 8) coupling component. This test was carried out in order to detect the presence of the diazonium ion in the solution by coupling to form an azo dye, the spectrum of which was to be compared with that of a sample of dye produced on a preparative scale (see chapter 6, page 169). This dye was a dark blue colour and so the yellow colour could not be attributed to this. 2-Amino-5-nitrothiazole itself is a yellow powder but a neutral solution of similar concentration to that of the reaction mixture was a very pale yellow, not as intense as the buffered reaction solution. However, this evidence is obviously not conclusive and further studies would be required to establish the nature of this yellow compound. This was not followed up in the present work since the solutions used to monitor the reaction became colourless (from the very pale yellow of the thiazole) and could be coupled without the yellow colouration appearing.

4.4 3-Amino-1,2,4-triazole

C-amino-1,2,4-triazoles behave as normal aromatic amines and are diazotised in aqueous mineral acids, forming diazonium salts which couple with aromatic amines and phenols[20,21]. Dyes derived from 1,2,4-triazoles have proven useful for polyester and polyacrilonitrile fabrics[22]. The ring N-H bond in the diazonium ion is reported[23] to be highly acidic and its pK_a has been measured[24] as 0.3 at 0°C. As mentioned earlier, aminoheteroaromatics containing such an acidic proton form diazo compounds on reaction with nitrous acid, and this has been observed in the case of 3-amino-1,2,4-triazole[24]:



(I)

Villarrassa[24], et al, have studied acid-base equilibria in diazo-azoles, including 3-amino-1,2,4-triazole, and report that (I), above, exhibits a UV absorption at 281nm. This was observed in the spectra of the reaction solutions in the present work and, in fact, the appearance of this peak was used to follow the reaction.

The order with respect to nitrous acid was shown to be unity and the data are presented in the following table.

4.4.1 Acid Catalysed Diazotisation

Reactions were carried out under first-order conditions ($[HNO_2] >> [Amine]$) and the kinetic equation derived for 2-amino-5-nitro-

Table 4.9 Nitrous Acid Dependence

$[Amino] = 7.98 \times 10^{-5}M$ $\lambda = 280nm$

$10^2[HNO_2]/M$	$10^2[H^+]_F/M$	$10^3 k_o/s^{-1}$
1.17	4.83	2.49 ± 0.034
2.33	4.77	6.32 ± 0.130
4.67	4.83	13.2 ± 0.250

thiazole (page 92) applies here since for 3-amino-1,2,4-triazole a non-zero intercept is observed, which indicates that both neutral and protonated forms undergo reaction:

$$k_o = \frac{k_3 K_a [HNO_2]_T[H^+]}{[H^+] + K_a} + \frac{k_3^+ [HNO_2]_T[H^+]^2}{[H^+] + K_a} \quad \ldots(4.6)$$

The K_a value for 3-amino-1,2,4-triazole has been determined[25] as $6.8 \times 10^{-5}M$ (imino-nitrogen) and so $[H^+] >> K_a$ throughout the acid range (table 4.10). Equation 4.6, then, becomes:

$$k_o = k_3 K_a [HNO_2]_T + k_3^+ [HNO_2]_T [H^+]$$

and a linear dependence of k_o upon $[H^+]$ is predicted. This linear dependence was observed experimentally and from the slope and intercept of the plot (fig. 4.5) the rate constants are:

$k_3 = 1620\ mol^{-2}dm^6s^{-1}$ and $k_3^{\pm} = 3.02\ mol^{-2}dm^6s^{-1}$ at 25°C

This qualitative difference is expected since in the protonated molecule the amino group is much less basic and hence less reactive. The amino-nitrogen in amino-heterocycles is generally weakly basic due to the electron-withdrawing effects of the heteroatoms, and the basicity is reduced further in this case by N-endocyclic protonation.

Table 4.10 3-Amino-1,2,4-triazole - Acid Catalysis

$[Amine] = 5.63 \times 10^{-5}M$ $[HNO_2] = 5.01 \times 10^{-2}M$ $\lambda = 280nm$

$10^2[H^+]/M$	$10^2k_o/s^{-1}$
2.22	1.07 ± 0.01
4.63	1.29 ± 0.01
7.04	1.58 ± 0.03
9.45	1.98 ± 0.03
11.9	2.33 ± 0.05
14.3	2.74 ± 0.05

SLOPE = $0.151\ mol^{-1}dm^3s^{-1}$

INT. = $5.53 \times 10^{-3}\ s^{-1}$

(FIG. 4.5)

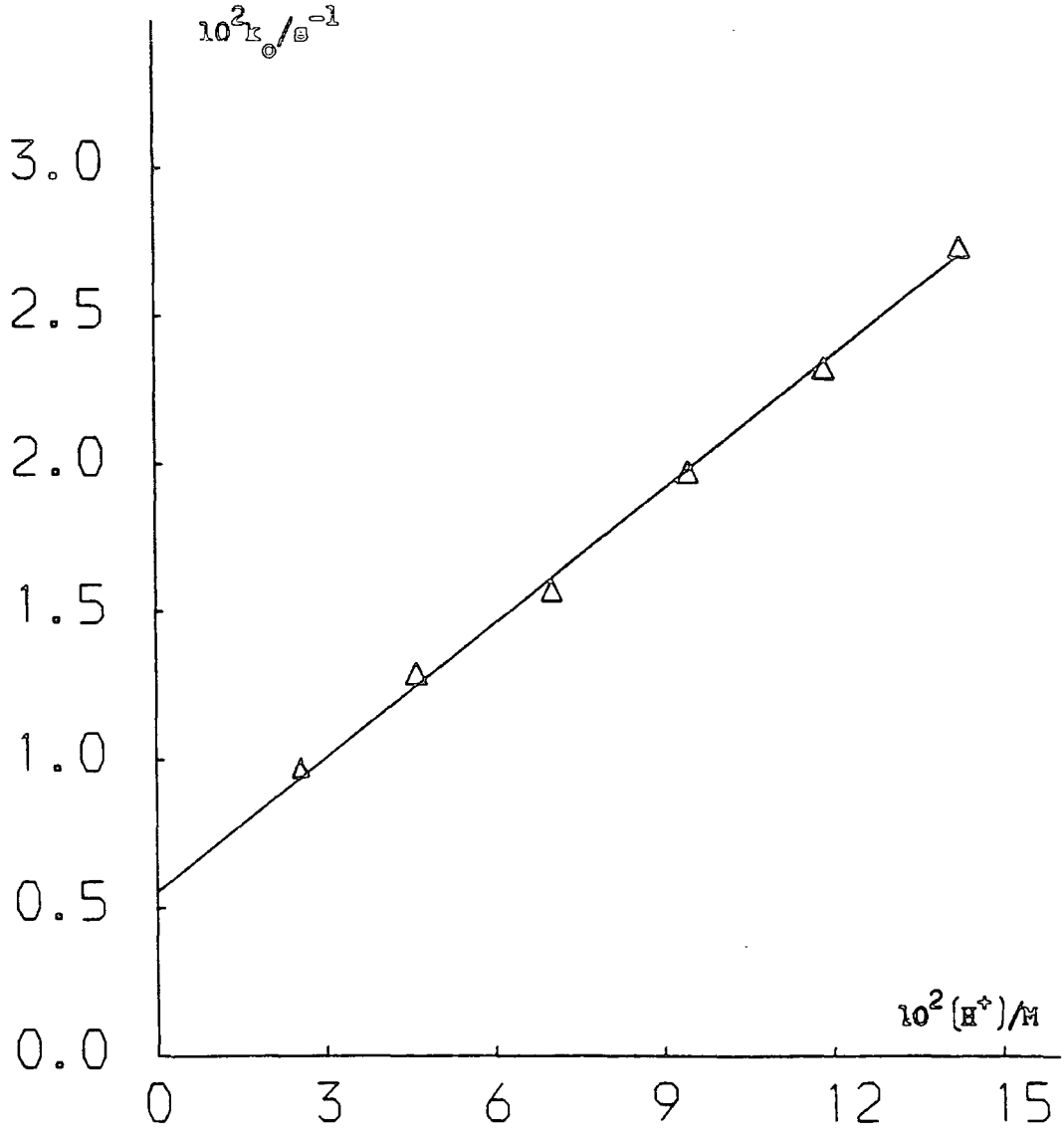
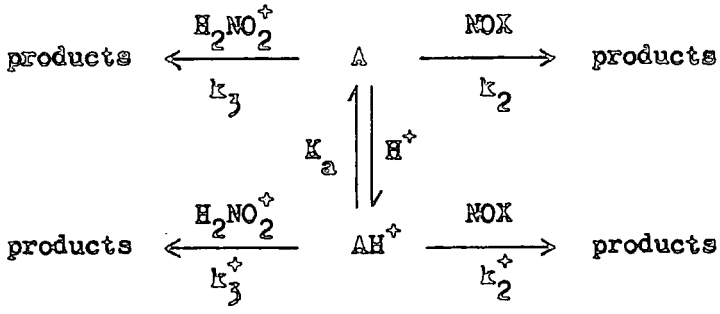


FIG. 4.5 — Acid Catalysed Diazotisation of 3-Amino-1,2,4-triazole.

4.4.2 Catalysis by Bromide and Thiocyanate

As is the case for the aniline derivatives - and many other substrates - diazotisation of 3-amino-1,2,4-triazole has been found to be subject to catalysis by bromide and thiocyanate. The reaction takes place via the intermediate formation of the corresponding NOX species, as described in chapter 1, section 1.5, and involves either the neutral amine or the N-endocyclic protonated form. There are thus four possible pathways, as shown below.



By taking into consideration the protonation equilibrium involving A and AH^+, and also the equilibrium for formation of NOX, equation 4.7 can be derived:

$$k_o = (k_3K_a + k_3^+[H^+] + k_2K_aK_{NOX}[X^-] + k_2^+K_{NOX}[H^+][X^-])\frac{[H^+][HNO_2]_T}{[H^+] + K_a}$$

.....(4.7)

The first two terms in this equation represent the acid catalysed

routes described in the previous section, the second two represent the nucleophile catalysed routes. Since $[H^+] \gg K_a$ under the present conditions ($[H^+] > 0.01M$) this equation simplifies to:

$$k_o = (k_2^+[H^+] + k_2K_a)[HNO_2]_T[X^-]K_{NOX} + (k_3K_a + k_3^+[H^+])[HNO_2]_T \quad .....(4.8)$$

Plots of k_o vs $[X^-]$ were linear for both bromide and thiocyanate.

Table 4.11 3-Amino-1,2,4-triazole - Bromide Catalysis

$[Amine] = 5.63 \times 10^{-5}M$ $[H^+] = 0.135M$ $[HNO_2] = 5.01 \times 10^{-2}M$

$10 \times [Br^-]/M$	$10^2k_o/s^{-1}$
0.150	3.13 ± 0.04
0.747	4.35 ± 0.05
1.50	6.04 ± 0.20
2.24	7.52 ± 0.08

SLOPE = 0.212 $mol^{-1}dm^3s^{-1}$

INT. = 0.0281 s^{-1}

(FIG. 4.6)

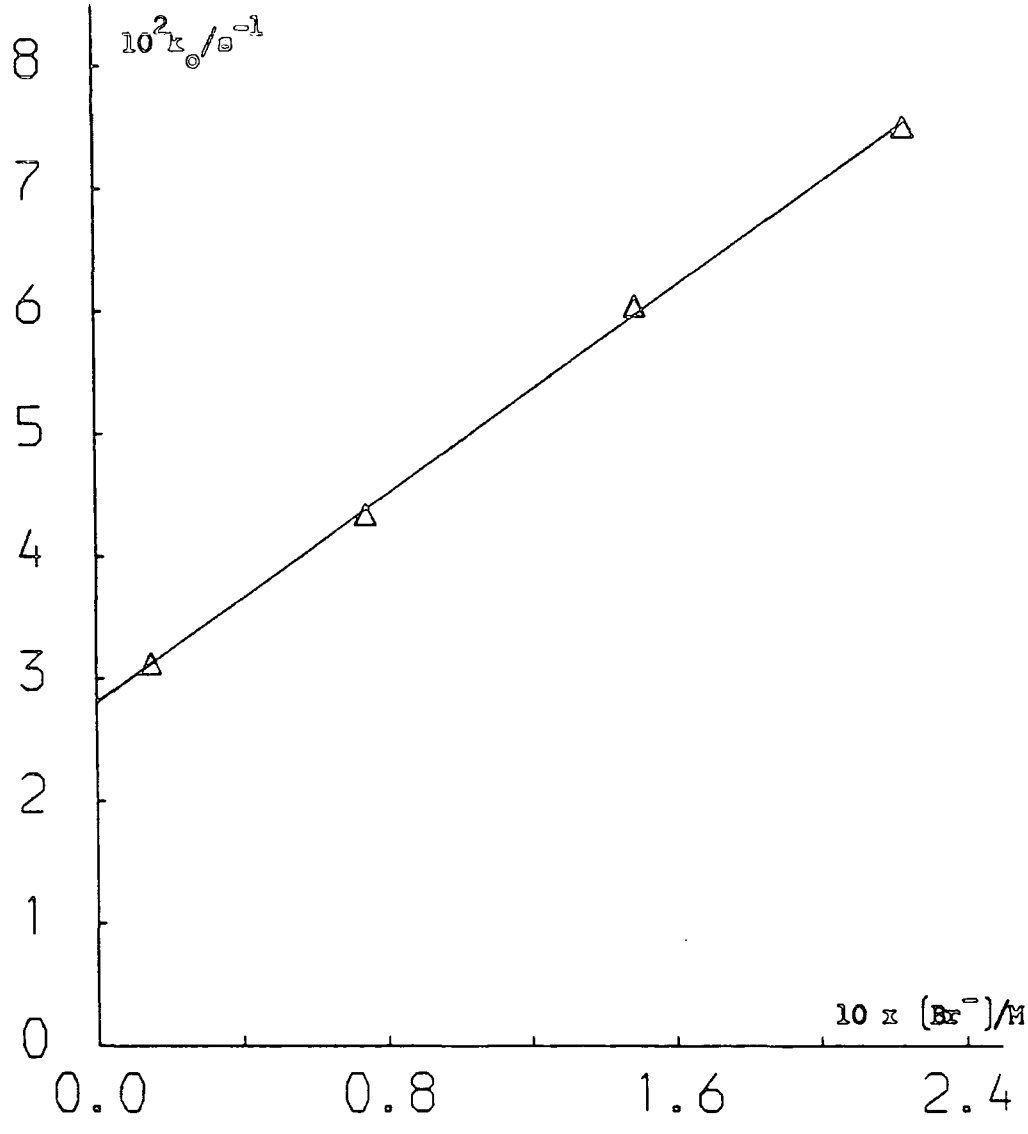


FIG. 4.6 — Bromide Catalysed Diazotisation of 3-Amino-1,2,4-triazole.

Table 4.12 3-Amino-1,2,4-triazole - Thiocyanate Catalysis

$[Amino] = 1.24 \times 10^{-4}$M $\quad [H^+] = 1.20 \times 10^{-2}$M $\quad [HNO_2] = 9.96 \times 10^{-3}$M

$10^2[SCN^-]/M$	$10^3 k_o/s^{-1}$
0.558	2.35 ± 0.05
1.19	2.64 ± 0.04
2.54	4.24 ± 0.06
3.96	5.47 ± 0.06
5.34	6.92 ± 0.05

SLOPE = 9.77×10^{-2} mol^{-1}dm^{3}s^{-1}

INT. = 1.67×10^{-3} s^{-1}

(FIG. 4.7)

Unfortunately, since the slope of each plot is given by:

$$\text{Slope} = (k_2^+[H^+] + k_2K_a)[HNO_2]_T K_{NOX}$$

we are not in a position to evaluate the individual rate constants k_2 and k_2^+. These may be determined by varying the acid concentration in the presence of a constant concentration of the nucleophile X^-, as described in the following section. The above data do, however, allow the calculation of the intercept of the k_o vs $[X^-]$ plot for each

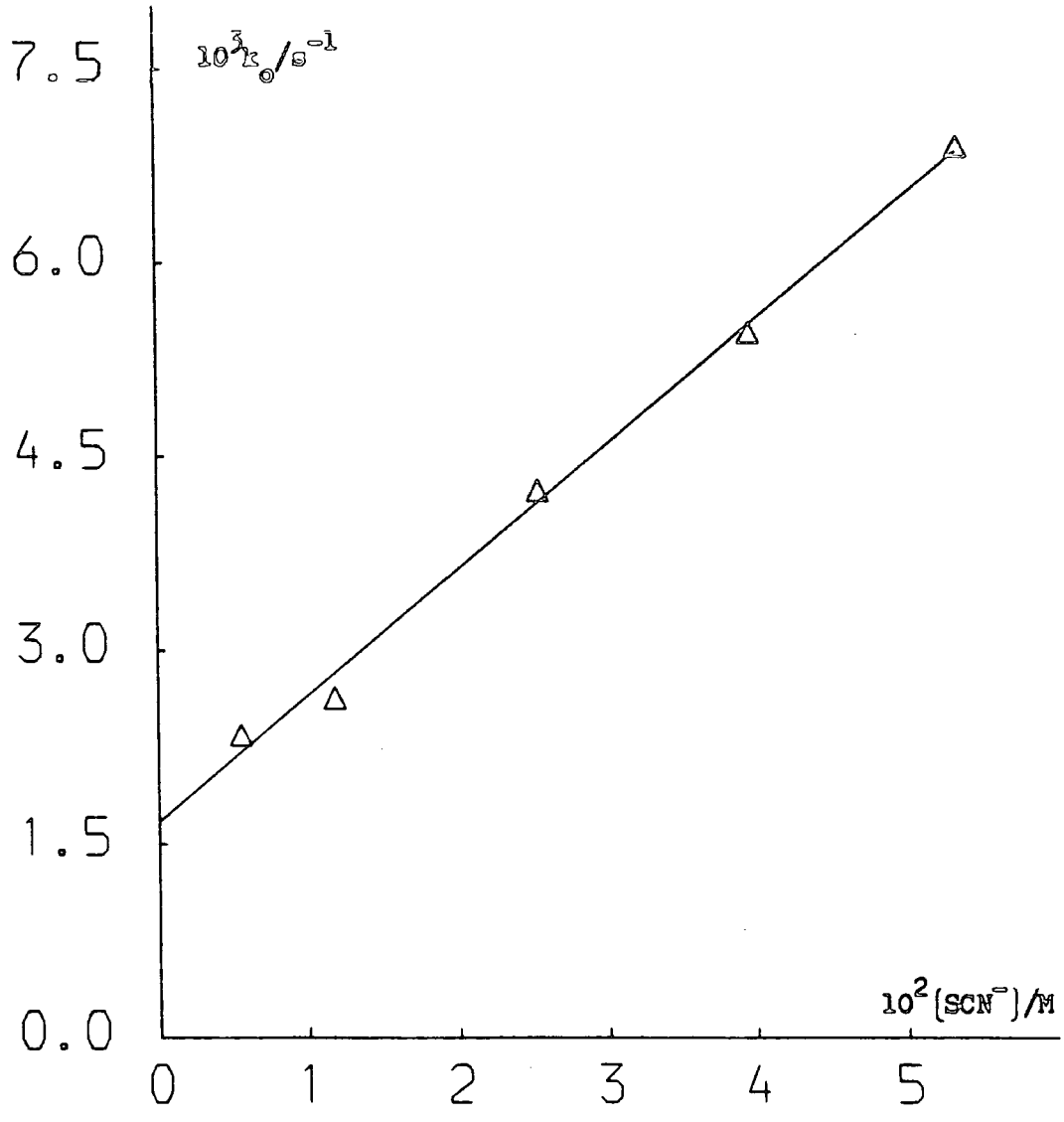


FIG. 4.7 — SCN^- Catalysed Diazotisation of 3-Amino-1,2,4-triazole.

nucleophile and this provides a test of the reliability of the k_3 and k_3^+ values determined in section 4.4.1. The intercept is given by:

$$INT. = (k_3K_a + k_3^+[H^+])[HNO_2]_T$$

For bromide catalysis the calculated intercept is $0.0259s^{-1}$ and for thiocyanate a value of $1.46 \times 10^{-3}s^{-1}$ is obtained. These are in excellent agreement with the experimental values of $0.0281s^{-1}$ and 1.67×10^{-3} s^{-1} respectively.

4.4.3 Acid Dependence in the Presence of Nucleophiles

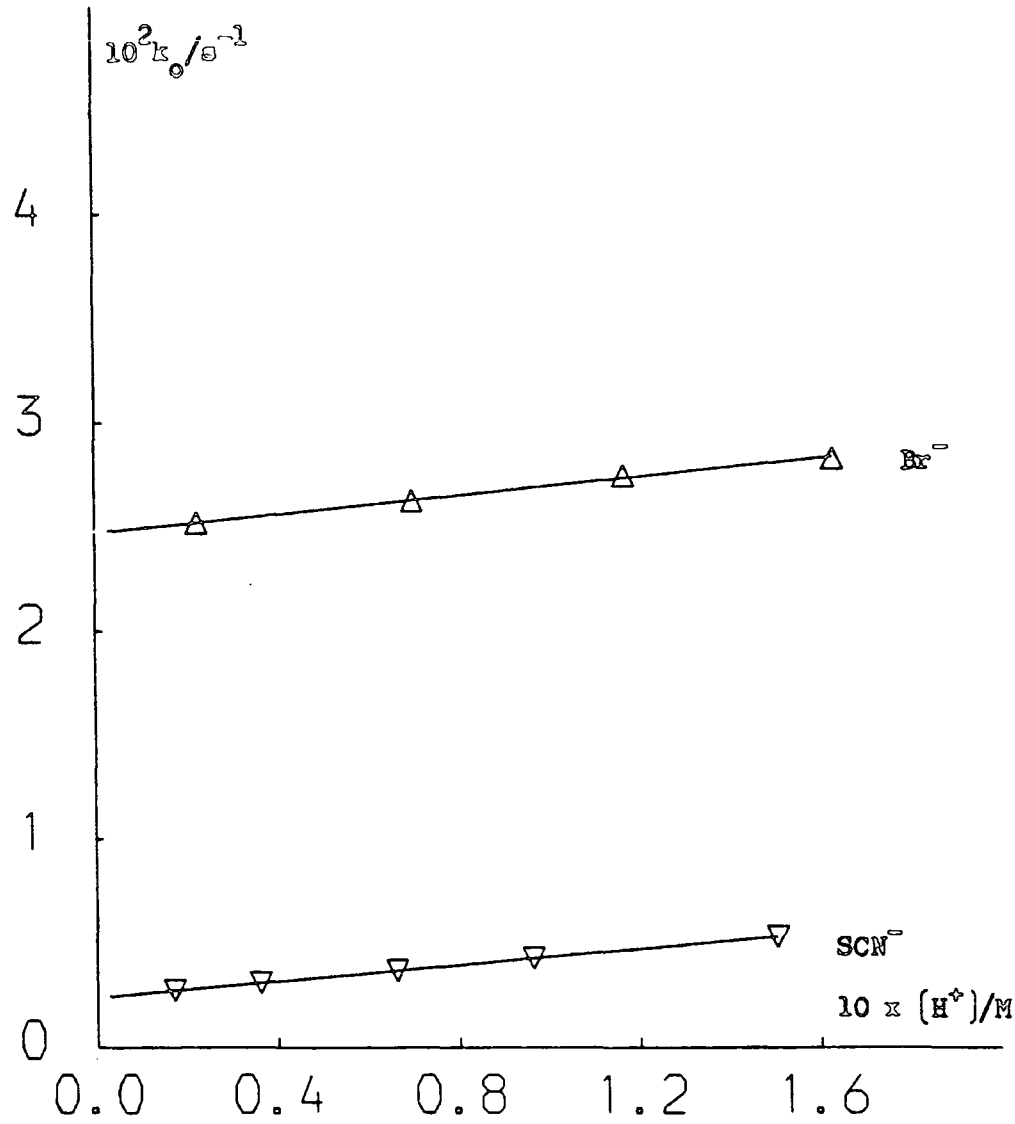
The acid catalysed reaction of 3-amino-1,2,4-triazole in the presence of a constant concentration of nucleophile was studied and the results are presented in the following tables.

Table 4.13 Acid Dependence at $[Br^-] = 0.197M$

$[Amine] = 9.88 \times 10^{-5}M$ $[HNO_2] = 2.03 \times 10^{-2}M$

$10 \times [H^+]/M$	$10^2k_o/s^{-1}$
0.227	2.52 ± 0.0966
0.702	2.63 ± 0.0928
1.17	2.75 ± 0.173
1.63	2.84 ± 0.0791

(FIG. 4.8)



▽ Thiocyanate

△ Bromide

FIG. 4.8 — Acid Dependence in the Presence of Constant [Nucleophile] for 3-Amino-1,2,4-triazole.

Table 4.14 Acid Dependence at $[SCN^-] = 8.97 \times 10^{-3}$M

$[Amine] = 1.21 \times 10^{-4}$M $\quad [HNO_2] = 9.96 \times 10^{-3}$M

$10^2[H^+]/M$	$10^2 k_o/s^{-1}$
0.173	0.273 ± 0.0072
0.363	0.311 ± 0.0099
0.663	0.370 ± 0.010
0.966	0.429 ± 0.013
1.50	0.535 ± 0.011

(FIG. 4.8)

Rearranging equation 4.8 we have:

$$k_o = (k_3^+ + k_2^+[X^-]K_{NOX})[H^+][HNO_2]_T + (k_3 + k_2[X^-]K_{NOX})[HNO_2]_T K_a$$

and from the plots of k_o vs $[H^+]$ for these reactions carried out in the presence of X^- we can determine the rate constants k_2 and k_2^+ in the above equation for both nucleophiles.

For reaction in the presence of each nucleophile linear plots of k_o vs $[H^+]$ were obtained (fig. 4.8). Referring to the above equation we have:

$$\text{Slope} = (k_3^* + k_2^*[X^-]K_{NOX})[HNO_2]_T$$

$$\text{Int.} = (k_3 + k_2[X^-]K_{NOX})[HNO_2]_T K_a$$

In the presence of Br^-:

$$\text{Slope} = 0.0277 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1}$$

$$\text{Int.} = 0.0247 \text{ s}^{-1}$$

and so the rate constants are:

$$k_2 = 1.62 \times 10^6 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1}$$

$$k_2^* = -189 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1} \quad \text{(negative)} \qquad \text{at } 25^\circ\text{C}$$

For thiocyanate:

$$\text{Slope} = 0.0197 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1}$$

$$\text{Int.} = 2.39 \times 10^{-3} \text{ s}^{-1}$$

which gives:

$$k_2 = 7.09 \times 10^3 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1}$$

$$k_2^* = -3.87 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1} \quad \text{(negative)} \qquad \text{at } 25^\circ\text{C}$$

Again the trend exhibited by the aniline derivatives in reactions with NOX species is the same here for reaction of the neutral amine; i.e. $k_{NOBr} > k_{NOSCN}$. The fact that negative rate constants have been obtained for reaction of the protonated amine can be attributed to the small values of the slopes of the plots. Any small error in these would result in large errors in the values of k_2^+. Since the intercepts are relatively large, particularly for Br^-, small errors will not have an appreciable effect on the values of k_2 which should therefore be reliable. Despite the negative rate constants the results indicate clearly that the non-protonated amine is the more reactive of the two forms and in fact it may be that $k_2^+ \simeq 0$. It is interesting to note that N-endocyclic protonation reduces the reactivity towards $H_2NO_2^+$ by a factor of about 500 and it may well be the case that this protonation is sufficient to reduce to zero the reactivity towards the weaker electrophile NOX. This adds weight to the suggestion that the thiazole undergoes reaction via the non-protonated form only, since the thiazole is a weaker base than the triazole. The situation is analogous to that of the aniline derivatives where reaction of $H_2NO_2^+/NO^+$ with the protonated amine can occur but there is no evidence to suggest that reaction occurs between NOX and $ArNH_3^+$ (i.e. $k_2^+ = 0$). The difference, though, is that protonation occurs at a site remote from the reaction centre in the triazole, a difference which is reflected by the fact that protonation in sulphanilic acid (for example) - i.e. protonation <u>at</u> the reaction centre - reduces the rate constant k_3 by a factor of 3000 (section 2.6, page 50). Assuming that $k_2^+ = 0$ for both NOBr and NOSCN the values of the slopes of the respective k_o vs $[X^-]$ plots are calculated to be

0.216 $mol^{-1}dm^3s^{-1}$ and 0.130 $mol^{-1}dm^3s^{-1}$, which are in good agreement with the experimentally determined values of 0.212 $mol^{-1}dm^3s^{-1}$ and 0.0977 $mol^{-1}dm^3s^{-1}$.

4.5 General Conclusions from Chapter 4

Perhaps the most important point to note in summarising the information presented in this chapter is that for these two substrates, and possibly for heteroaromatic primary amines in general, the kinetics of diazotisation are identical to those of the aniline derivatives. The reaction is catalysed by both acid and nucleophiles and for acid catalysis the protonated substrate undergoes reaction, although in these cases the protonation site is not the reaction site (unlike the aniline derivatives where the two can be the same). An investigation into the possibility of the reaction of the protonated amine with NOX showed that no reaction takes place for either the thiazole or the triazole.

It is of interest to compare the rate constants obtained in the acid catalysis studies with those for the substrates studied in the earlier chapters and also with those obtained by other workers. This comparison is made in table 4.15. Note the similarity between the values for the thiazole and 2,4-dinitroaniline, which is also deactivated by electron-withdrawing groups.

Table 4.15 Comparison of k_3 values for Nitrosation in Water at 25°C

Substrate	$k_3/dm^6 mol^{-2} s^{-1}$	Ref.
$CO(NH_2)_2$	0.89	26
2-Amino-5-nitrothiazole	2.19	this work
2,4-Dinitroaniline	2.50	this work
HN_3	160	26
$NH_3^+NH_2$	620	26
Sulphanilamide	900	this work
Glutathione	1080	27
Mercaptosuccinic acid	1334	28
3-Amino-1,2,4-triazole	1620	this work
Thioglycolic acid	2630	27
4-Nitroaniline	2700	this work
Sulphanilic acid	7300	this work

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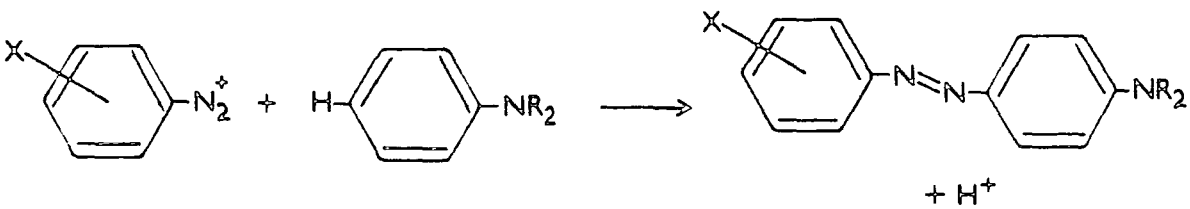
CHAPTER 5

'IPSO' - SUBSTITUTION in AZO - COUPLING REACTIONS

5.1 General Introduction to Coupling Reactions

By far the most important use of aromatic and heteroaromatic diazonium ions is in the manufacture of azo-dyestuffs, which are formed by coupling of a diazonium ion (commonly called the 'diazo component') at a ring carbon atom in an aromatic amine or phenol (the 'coupling component')[1,2]. The reaction is shown in scheme 5.1 using an aromatic amine as an example of a coupling component:



SCHEME 5.1

Diazonium ions are Lewis acids[2] and, depending on which atom in the coupling component donates the lone pair of electrons, coupling at nitrogen, oxygen, phosphorus, or sulphur can also occur[2]. The present work is concerned only with coupling at carbon, although the possibility of N-coupling will be discussed.

5.2 Acid-Base Pre-equilibria

It is a well established fact that the rates of all azo-coupling reactions are dependent upon the acidity of the reaction medium[3]. The first quantitative investigation of this dependence was made by Conant and Peterson[4] who demonstrated that the coupling rate of a series of

naphtholsulphonic acids is proportional to $[OH^-]$ over the pH range 4.5-9.2. They concluded that the substitution proper was preceded by an acid-base pre-equilibrium in one of the reactants and they attributed this to the diazo-component, suggesting that the reaction occurred between undissociated naphthol and diazohydroxide formed as follows:

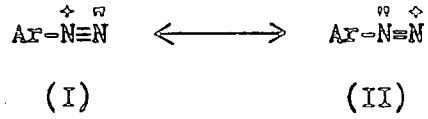
$$ArN_2^+ + OH^- \rightleftharpoons ArN{=}NOH$$

Wistar and Bartlett[5] later pointed out that the same pH dependence is obtained if the coupling component takes part in an acid-base pre-equilibrium:

$$ArOH + OH^- \rightleftharpoons ArO^- + H_2O$$

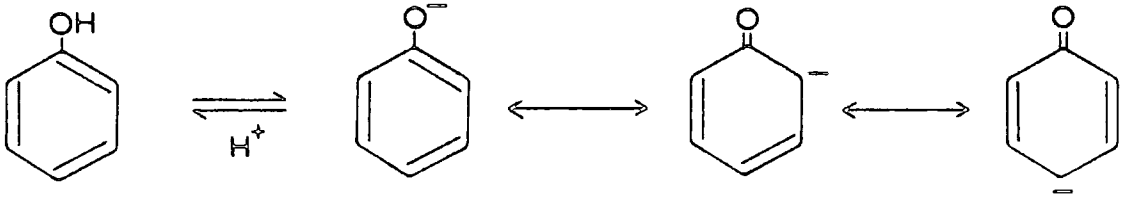
Subsequent work, particularly that of Zollinger and coworkers[6], showed clearly that the diazonium ion reacts with the naphtholate (or phenolate etc.) ion and with non-protonated aromatic amines. It is now common knowledge that electrophilic substitutions in general which take place via the most acidic equilibrium form of the electrophile and the most basic form of the nucleophilic substrate give rise to the highest rates of substitution[2].

In order to understand the greater reactivity of the phenolate or free amino coupling components it is necessary to consider the mesomeric limiting structures of the species participating in the reaction. As mentioned in chapter 1 (page 22), the diazonium ion may be represented by a resonance hybrid:

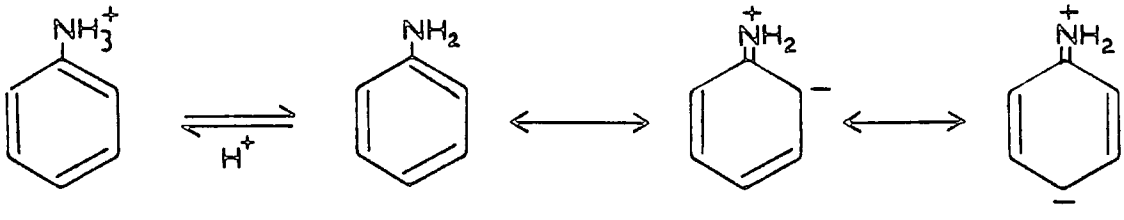


(I) (II)

The β nitrogen atom in structure II possesses only a sextet of electrons and is therefore strongly electrophilic. The limiting structures in the free phenol and phenolate ion show that the latter should provide the more reactive substrate for electrophilic substitutions:



Similarly, for amino coupling components, resonance occurs in the free base which is not possible in the protonated amine:



The greater reactivity of the phenolate ion compared with the free phenol has been demonstrated for a series of electrophilic substitutions, e.g. halogenation[7], hydroxymethylation[8], and deuteration[9]. The more marked difference in reactivity of the anilinium ion and free aniline has been demonstrated for bromination[10].

Thus, under optimum conditions, coupling of amine or phenol coupling components can be written as:

$$ArN_2^+ + ArNR_2 \longrightarrow ArN{=}NArNR_2 + H^+$$

$$ArN_2^+ + ArO^- \longrightarrow ArN{=}NArO^- + H^+$$

The optimum conditions for a particular reaction depend upon several factors including amine or phenol pK_a values and the presence of electron withdrawing or donating groups in the diazonium ion. In general the reaction rate is reduced at low pH due to protonation of the coupling component to form the much less reactive phenol or anilinium ion (naphthol or naphthylammonium ion, etc.). On the other hand too high a pH reduces the rate due to formation of the unreactive diazohydroxide, even though such conditions strongly favour the reactive form of the coupling component. The optimum pH for most reactions generally lies in the range 6 - 9. This is not usually the case, however, when the diazonium ion is derived from a heteroaromatic amine. For some such compounds increasing the pH of the diazonium ion solution prior to coupling results in the formation of the diazohydroxide which is in equilibrium with a stable primary nitrosamine[11] (see chapter 4, p87). Alternatively, for those heterocycles containing a labile hydrogen atom, removal of a proton from the diazonium ion, resulting in the formation of a diazo ($R{=}N_2$) compound,[12] is favoured by raising the pH (ch.4, p87). Thus, although the optimum pH range for reaction of aniline diazonium ions is 6 - 9, for heteroaromatic diazonium ions it is much lower. In most cases, though,

the reduction in the nucleophilic nature of the coupling component due to protonation is offset by the generally greater electrophilic strength of the diazonium ions relative to those derived from aniline derivatives[2].

5.3 The Ortho/Para Ratio in Azo-Coupling

In principle, coupling components in which the positions ortho- and para- to the directing substituent are free can be attacked at either (or both) by the diazo component and it is of technical importance to exploit the factors which influence the o/p ratio. For example, if coupling occurs ortho- to a phenolic -OH group, intramolecular hydrogen bonding can occur and this shifts the protolytic equilibrium into a region of pH (>11) which in practise is not reached by textiles dyed with these compounds[1b]. This is important from the standpoint of the dyestuffs industry since acid-base equilibria in azo-dyes can lead to colour changes (many indicators used in the laboratory are azo-dyes - methyl orange is an example). In the corresponding para-coupled dye this hydrogen bonding is not possible and so, due to the electron-withdrawing azo and (usually) sulphonate groups (which make the dye water-soluble), the pK_a of the phenolic -OH is lowered to about 7 - 9 which results in noticable colour changes when a dyed fabric is washed with soap[1b].

Phenol is one of the simplest examples of a coupling component capable of substitution in the ortho- and para- positions and the o/p ratio was investigated by Bamberger[13] as long ago as 1900. He found that in aqueous alkaline media the p-coupled dye was the major product, being formed in about 98% yield and accompanied by about 1% each of the ortho-

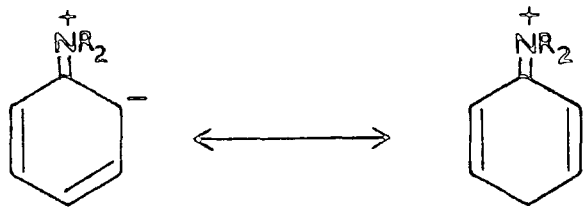
coupled and disazo-dyes. It has also been noted that 1-naphthol couples with benzenediazonium ion in acidic or weakly alkaline solutions almost exclusively (~99%) in the para-position[1b], whilst in strongly alkaline media considerable quantities of the 2,4-disazo-dye are formed[1b]. Many other studies were performed involving different types of diazonium ions and coupling components and the general conclusion arrived at as a result of this work was that the o/p ratio depends on several factors[1b]:

1) nature of the diazo component
2) nature of the solvent
3) pH of the medium
4) temperature
5) presence of catalysts (bases)
6) position of substituents

Recently, Zollinger and coworkers[14] have shown that the o/p ratio can also be affected by mixing and diffusion effects. Amino compounds involved in coupling reactions behave in an analogous manner to the phenol and naphthol coupling components, but no clear-cut rules can be laid down to predict the product ratios for any of these compounds.

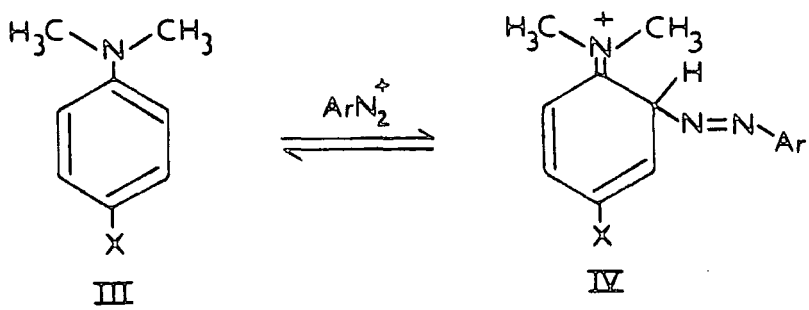
The present work is concerned with coupling to N,N-dimethylaniline derivatives and the desired product is the para-coupled dye, so it is necessary to consider the possibility of ortho-coupling. This will be discussed quantitatively in the next section and so it is sufficient here to consider the qualitative aspects.

As mentioned earlier, the important mesomeric limiting structures for aniline derivatives are:



I II

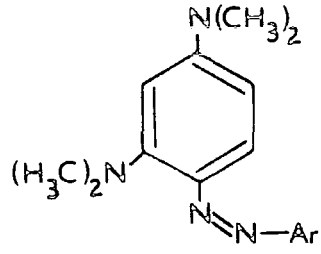
and it would seem that ortho- and para-coupling are both highly likely. However, it has been known for some time that ortho-coupling in N,N-dimethylaniline derivatives occurs with great difficulty[15] and this is explained by steric hindrance in the intermediate IV, below. Both methyl groups must lie in the plane of the benzene ring and thus form an obstruction to the addition of the diazonium ion as it approaches the ortho-position.



III IV

The fact that 1,3-bisdimethylaminobenzene couples in the 4-position (V, below) seems to contradict this interpretation but is easily understood by assuming that coupling occurs para- to the dimethylamino group which takes part in the resonance shown above. The other dimethylamino group cannot take part in this resonance and so the methyl groups do not

have to lie in the plane of the ring.



(V)

5.4 'IPSO'-Coupling

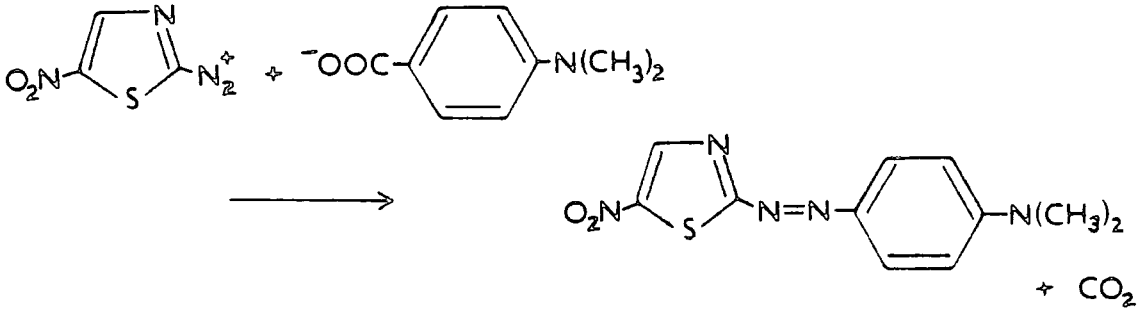
The preference for p-substitution in the coupling of benzene derivatives is so strong that the entering diazonium ion will even displace another substituent already present if it can be ejected as a cation of not too high energy[16]. There is now a growing interest in these electrophilic aromatic substitution reactions in which the leaving group is other than hydrogen[17,18]. The electrophile, $E^{\oplus}$, in the present case is the diazonium ion, which attacks the substituted coupling component at the substituent ('ipso') position:

$$ArX + E^{\oplus} \longrightarrow ArE + X^{\oplus}$$

Ipso-coupling is a fairly recent arrival on the dyestuffs scene. Many azo-dyes which are highly commercially acceptable are difficult to produce in good yields and purity by conventional means[19]. Normally a coupling component can be substituted in the 2,3,5, or 6 positions but not in the 4-position since this is the position at which electrophilic attack generally occurs and, according to standard coupling procedure, must remain free. It has been discovered[19], however, that if certain

substituents are introduced into the coupling position, coupling occurs with the elimination of the substituent, resulting in the formation of the same dye as would have been obtained had the substituent not been present, and in many cases with greater yield and purity.

In a recent patent[19], Shuttleworth reports that the yield in azo-coupling reactions of the diazonium ion derived from 2-amino-5-nitro-thiazole with N,N-dimethylaniline and related coupling components is never more than about 50%. The yield can be significantly increased if 4-N,N-dimethylaminobenzoic acid is used instead of N,N-dimethylaniline itself. The leaving group here is CO_2, since the proton of the carb-oxylic acid group is already dissociated in a pre-equilibrium.



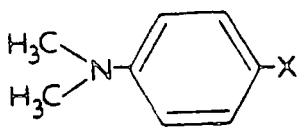
In a conventional electrophilic aromatic substitution the leaving group hydrogen is released as a proton i.e. as a Lewis acid, leaving behind the pair of σ electrons on the aromatic substrate. In principle, therefore, all substituents which readily form electrophilic (or stable neutral) species are capable of being replaced by electrophilic reagents, in this case a diazonium ion. An example of this is the coupling of 4-hydroxybenzoic acid in which the carboxylate ($-COO^-$) leaves as CO_2 (see above) and in fact the reaction occurs more readily than coupling in the ortho-position with elimination of a proton[20].

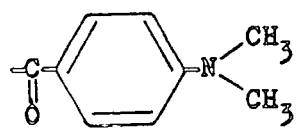
Fischer and Zollinger[18] have studied the rates of substitution of the groups X in 1-X-2-naphthol-6-sulphonic acid, where X = H, Cl, Br, and I. they found that the rates of substitution of the halogens relative to hydrogen were 0.0070 : 0.0089 : 0.149 for X = Cl, Br, and I respectively. Thiosulphate catalysis was found in the reaction of 1-bromo-2-naphthol-6-sulphonic acid but, rather surprisingly, reactions of the corresponding chloro- and iodo- compounds were not catalysed. It was pointed out that this indicates that the relative rate observed represents an apparent order of leaving ability.

Colonna, et al[21], have studied the coupling reactions of various substituted indoles and N,N-dimethylanilines with 4-nitrobenzenediazonium ion. They provided experimental evidence that radical pairs can be detected in ipso-coupling reactions. Some of their work is particularly relevant to the study reported in this chapter and a fuller discussion of it is left until later.

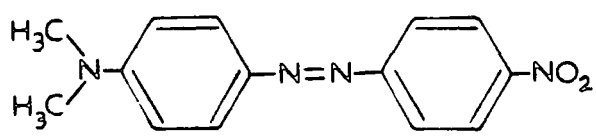
5.4.1 Scope of the Present Work

The purpose of the present study was to examine kinetically the coupling reactions of various 4-substituted N,N-dimethylanilines and attempt to establish the relative leaving abilities of the ipso-substituents. The diazonium ion chosen was that derived from 4-nitroaniline since this has the highest electron affinity of the monosubstituted diazonium ions[22] and could be expected to produce good yields. The various leaving groups are shown below. These groups were expected to represent a good range of leaving abilities, the groups -COOH and $-SO_3H$ (actually $-COO^-$ and $-SO_3^-$ under the prevailing reaction conditions)



X
-H
$-COO^-$
$-SO_3^-$
$-COCH_3$
-CHO

$-CH_3$

leaving readily as the neutral molecules CO_2 and SO_3, and the group $-CH_3$ leaving with great difficulty, if at all. The other groups were expected to be intermediate between these two extremes. The common product from all of these reactions was expected to be the azo-dye shown below.



The reaction conditions and the method used for this study are presented in chapter 6. The data obtained are tabulated below and shown graphically in fig 5.1.

5.4.2 Tables of Data

As described in detail in chapter 6, reactions were carried out under first-order conditions with [coupler] >> [diazonium ion]. The solutions were buffered to pH ~ 7.9.

Table 5.1 X = H

$[ArN_2^+] = 1.06 \times 10^{-4}$ M $\lambda = 605$nm pH = 7.89

10^2[coupler]/M	k_o/s^{-1}
0.490	0.997 ± 0.021
0.981	2.10 ± 0.094
1.47	2.95 ± 0.10
1.96	3.95 ± 0.14
2.45	4.99 ± 0.22
5.02	10.3 ± 0.43

SLOPE = 204 $M^{-1}s^{-1}$

INT. = 2.04×10^{-3} s^{-1}

Table 5.2 K = $-COO^-$

$[ArN_2^+] = 1.06 \times 10^{-4}$ M λ = 590 - 610nm pH = 7.87

10^2 [coupler]/M	k_o/s^{-1}
0.261	0.190 ± 0.006
0.419	0.262 ± 0.011
0.521	0.316 ± 0.012
1.04	0.477 ± 0.019
1.60	0.698 ± 0.023
2.08	0.874 ± 0.036

SLOPE = 36.8 $M^{-1}s^{-1}$

INT. = 0.106 s^{-1}

Table 5.3 $X = -SO_3^-$

$[ArN_2^+] = 1.06 \times 10^{-4} M$ $\lambda = 560nm$ pH = 7.85

$10^2[coupler]/M$	k_o/s^{-1}
0.523	0.0939 ± 0.0033
1.05	0.110 ± 0.036
1.57	0.122 ± 0.045
2.09	0.126 ± 0.075
2.62	0.138 ± 0.077

SLOPE = 1.99 $M^{-1}s^{-1}$

INT. = 0.0867 s^{-1}

Table 5.4 X = $-\overset{O}{\overset{\|}{C}}CH_3$

$[ArN_2^+] = 1.06 \times 10^{-4}$ M λ = 510nm pH = 7.89

10^2[coupler]/M	$10^2 k_o / s^{-1}$
0.480	6.89 ± 0.37
0.959	7.04 ± 0.40
1.44	7.33 ± 0.43
1.92	7.37 ± 0.41
2.40	7.64 ± 0.44

SLOPE = 0.302 $M^{-1} s^{-1}$

INT. = 0.0670 s^{-1}

Table 5.5 X = $-\overset{O}{\overset{\|}{C}}-H$

$[ArN_2^+]$ = 1.06 x 10^{-3} M λ = 550nm pH = 7.88

10 x [coupler]/M	$10^3 k_o/s^{-1}$
0.356	3.39 ± 0.22
0.712	4.80 ± 0.26
1.07	7.64 ± 0.29
1.42	8.15 ± 0.38

SLOPE = 0.0481 $M^{-1}s^{-1}$

INT. = 1.72 x 10^{-3} s^{-1}

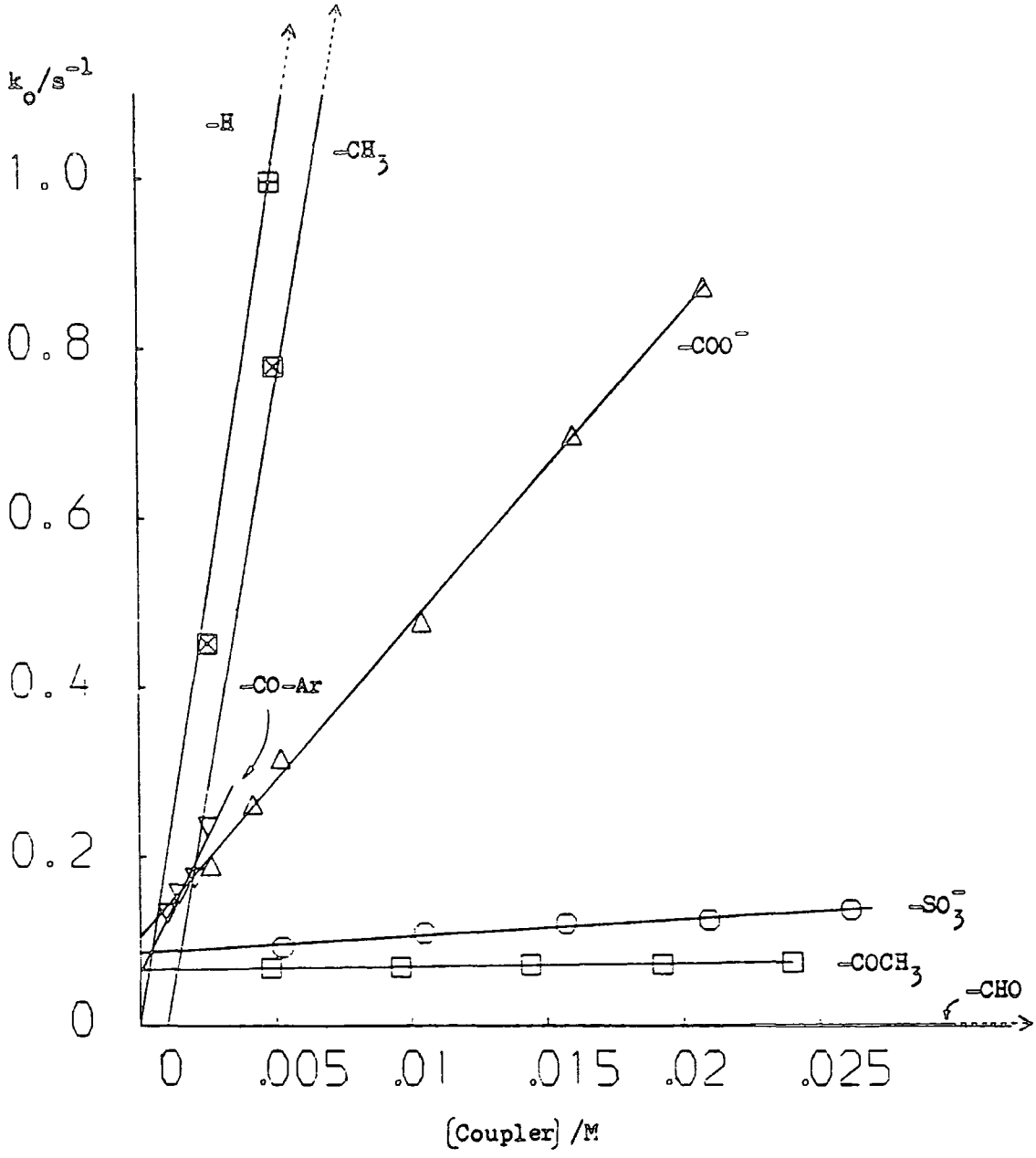
Table 5.6 X = $-\overset{O}{\overset{\|}{C}}-C_6H_4-NMe_2$

$[ArN_2^+]$ = 1.06 x 10^{-4} M λ = 500nm pH = 7.90

10^3[coupler]/M	k_o/s^{-1}
1.00	0.133 ± 0.058
1.43	0.157 ± 0.083
2.00	0.175 ± 0.077
2.51	0.236 ± 0.098

SLOPE = 64.4 $M^{-1}s^{-1}$

INT. = 0.0633 s^{-1}



Variation of Reaction Rate with [4-X-N,N-dimethylaniline]

Table 5.7 $X = -CH_3$

$[ArN_2^+] = 1.06 \times 10^{-4}$ M $\lambda = 550$nm pH = 7.90

$10^2[\text{coupler}]/M$	k_o/s^{-1}
0.500	0.778 ± 0.061
1.01	1.55 ± 0.077
2.02	3.47 ± 0.12
3.02	5.56 ± 0.32

SLOPE = 185 $M^{-1}s^{-1}$

INT. = -0.183 s^{-1}

5.4.3 Kinetic Analysis

The mechanism of ipso-coupling, as already stated, appears to be the same as that for conventional coupling[2] but with elimination of the substituent X^+ rather than H^+.

$$ArX + Ar'N_2^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[Ar(X)N{=}NAr' \right]^+$$

$$\left[Ar(X)N{=}NAr' \right]^+ + B \xrightarrow{k_2} ArN{=}NAr' + BX^+$$

where B is a base, usually the solvent. The rate equation derived from this scheme, by applying a steady-state approximation to $\left[Ar(X)N{=}NAr'\right]^{\ddagger}$ is:

$$\text{RATE} = \frac{k_1 k_2 [ArX][ArN_2^{\ddagger}][B]}{(k_{-1} + k_2[B])}$$

and under first-order conditions ($[ArX] >> [ArN_2^{\ddagger}]$) we have:

$$k_o = \frac{k_1 k_2 [ArX][B]}{(k_{-1} + k_2[B])}$$

Clearly there are two possible limiting forms here:

(a) $k_{-1} >> k_2[B]$ in which case we have:

$$k_o = \frac{k_1 k_2}{k_{-1}}[ArX][B]$$

(b) $k_{-1} << k_2[B]$ which gives:

$$k_o = k_1[ArX]$$

In any case, whichever of these three equations applies, we essentially have:

$$k_o = m[ArX]$$

where $m = k_1k_2[B]/k_{-1}$ as in (a), or $m = k_1$ as in (b), or $m = k_1k_2[B]/(k_{-1} + k_2[B])$ as in the intermediate situation. Thus one would expect a first-order dependence on $[ArX]$ for all three. Linear plots of k_o vs $[ArX]$ were obtained for all substrates and for $X = H$ and $X = CH_3$ zero intercepts were observed. However, for the other substrates non-zero intercepts were observed and this is difficult to explain using the above equations which predict linear plots passing through the origin.

If in these cases we assume that the base which interacts with the steady-state intermediate is not a water molecule but a second molecule of the substrate itself then we obtain:

$$k_o = \frac{k_1k_2[ArX]^2}{(k_{-1} + k_2[ArX])}$$

Here we can see that if $k_{-1} >> k_2[ArX]$ we have:

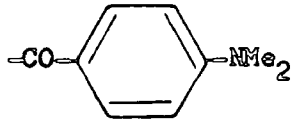
$$k_o = \frac{k_1k_2}{k_{-1}}[ArX]^2$$

and, if by increasing $[ArX]$ the condition $k_{-1} << k_2[ArX]$ is satisfied we have:

$$k_o = k_1[ArX] \qquad (5.1)$$

From this it can be seen that a plot of k_o vs $[ArX]$ would have a steep

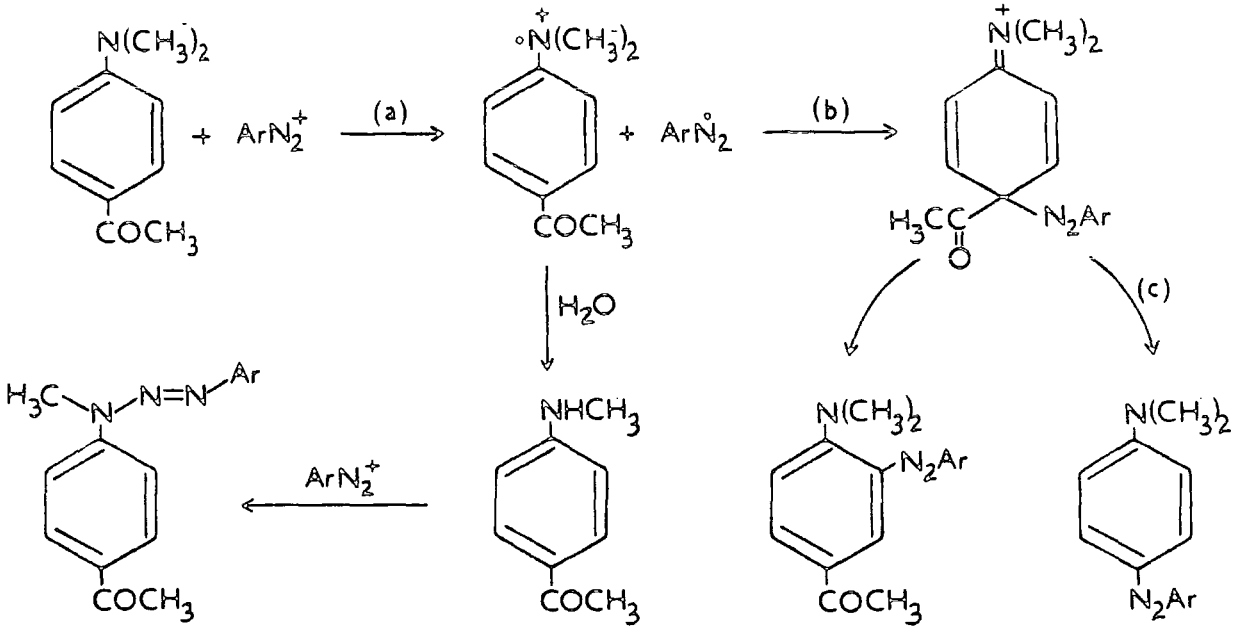
slope initially at low [ArX] but would curve and eventually become linear with positive slope as the condition $k_{-1} << k_2[ArX]$ is satisfied and 5.1 becomes applicable. Extrapolating back to the k_ψ axis would then give a positive intercept. This assumption that the coupling component acts as a base is not unreasonable since catalysis by organic bases (e.g. pyridine) has been demonstrated previously in azo-coupling reactions[23]. Assuming that this explanation is correct, then, we can obtain the values of k_1 for these substrates from the slopes of the plots. Thus we have:

X	$k_1/M^{-1}s^{-1}$
-H	204
$-COO^-$	36.8
$-SO_3^-$	1.99
$-COCH_3$	0.302
-CHO	0.0481
	64.4
$-CH_3$	185

There are two points worthy of note here. Firstly the rate constant for attack of the diazonium ion on the compound with X = $-CO-C_6H_4-NMe_2$ is

about 200 times greater than that for the similar (and less bulky) group X = $-CO-CH_3$. This may be explained by the fact that, because of its low solubility, only very weak solutions of this compound ($X = -CO-C_6H_4NMe_2$) could be obtained. The concentration range was 10^{-3} - 2.5×10^{-3}M and it is possible that in this range $k_{-1} \sim k_2[ArX]$ applies, or perhaps even $k_{-1} >> k_2[ArX]$, which would result in a steep initial slope, as observed. The second point to note is the large k_1 value for attack on the methyl-substituted coupling component ($X = -CH_3$) despite the fact that alkyl groups generally tend to be poor leaving groups. It is more likely that in this case substitution occurs not at the ipso-position but at the position ortho- to the N,N-dimethylamino group, even though this is hindered by the N-methyl groups themselves. This would, of course, result in elimination of H^+ and one might expect a rate constant similar in magnitude to that for para-coupling where X = H. It is also possible in this case that coupling occurs at the amino-nitrogen rather than at carbon, as has been observed in other cases[24]. Some evidence in support of this was obtained and will be dealt with in the next section.

Colonna et al[21] have studied the ipso-substitution reactions of various N,N-dimethylaniline derivatives and in the case of the compound with $X = -CO-CH_3$ they found that monodemethylation and N-coupling had occurred. They postulated a mechanism involving the intermediate formation of a radical cation, as shown in the following scheme. Their argument in support of this was based on product analysis and the fact that anodic and chemical oxidation studies have shown that demethylation of N,N-dimethylanilines is a reaction involving the intermediate formation



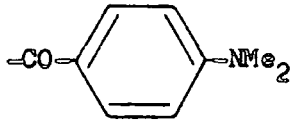
(Ar = $C_6H_4NO_2$-p) SCHEME 5.2

of a radical cation[25,26]. They also suggested that the formation of the ipso-coupled product (with no accompanying demethylation or N-coupling) also involves a radical cation (steps a, b, & c above). However, Penton and Zollinger[27] were able to observe monodemethylation during coupling only in very dry acetonitrile and Zollinger points out[2] that the product analysis studies of Colonna et al may be insufficient evidence to support their argument.

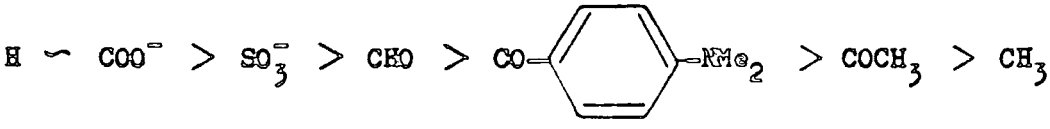
Since the values of k_1 derived above refer to the attack of the diazonium ion at the ipso- position, and not to the leaving ability of the group X, an idea of the relative leaving abilities of the ipso-substituents can be gained from measurements of the yield of the desired ipso-coupled product. Yield measurements were carried out using HPLC and the data obtained are presented below.

5.4.4 Yield Measurements

Using HPLC it was possible to measure ipso-coupled-dye yields with good precision using the peak integration values obtained from chromatographed reaction solutions. The method used is described fully in section 6.7.7. The yields obtained are shown in the following table.

X	Yield/%
-H	67
$-COO^-$	68
$-SO_3^-$	21
$-COCH_3$	0.2
-CHO	1.1
	0.7
$-CH_3$	~ 0

From this it would seem that the best leaving groups are X = H and $X = COO^-$ under these conditions, since the highest yield of dye was obtained in these cases, and the poorest is $X = CH_3$. The results suggest the following order of leaving ability:



In the case of X = CH_3 no peak due to the ipso-coupled dye was observed in the chromatograms of the reaction mixtures. Two other peaks approximately equal in intensity were observed and the solutions were bright red in colour, similar to the ipso-coupled solutions but much deeper. It is possible that these two products were ortho-coupled dye (hence the bright red colour) and the N-coupled (N-demethylated) compound. The evidence for this is not conclusive and a full product analysis would be necessary in order to identify these compounds. However, the red coloration together with the similarity between the rate constants for attack of the diazonium ion on the compounds with X = CH_3 and X = H suggest that ortho-coupling has occurred.

Colonna et al[21] report that for X = $COCH_3$ and X = CHO yields of 6% and 60% respectively were obtained in reactions with 4-nitrobenzenediazonium ion. They give no indication of the coupling component concentrations in their reactions, which were carried out in aqueous ethanol rather than aqueous acetone as in the present study, and they give no indication of the pH of their reaction media. Therefore it is difficult to compare these data quantitatively. In the case of the compound with X = $COCH_3$, though, they found that the ipso-coupled dye was not the major product (see scheme 5.2), and this was also noted in the present work, a larger peak appearing at a shorter retention time in the HPLC chromatogram. A peak was observed with the same retention time for X = CHO and X = $-CO-C_6H_4-NMe_2$ also, but here the ipso-coupled dye was the major product. For those compounds with low yields the signal/noise ratio in the chromatograms was low and was particularly bad for X = $COCH_3$, meaning that the yields determined in these cases are subject

to some error. The following table shows the dependence of the yield on the concentration of coupling component.

	-H	$-COO^-$	$-SO_3^-$	$-COCH_3$	-CHO	-CO-Ar
10^3[Coupler]/M	4.91	1.97	1.99	10.1	75.8	2.66
Yield/%	62.3	64.6	15.9	0.28	5.40	1.20
10^3[Coupler]/M	2.46	0.98	0.99	5.05	37.9	1.33
Yield/%	66.1	61.8	13.9	0.130	3.60	0.62
10^3[Coupler]/M	1.23	0.49	0.49	2.53	19.0	0.665
Yield/%	63.8	62.4	11.0	0.11	2.00	0.30
	$[ArN_2^+] = 1.02 \times 10^{-4}$M			$[ArN_2^+] = 5.10 \times 10^{-4}$M		

The concentration of the diazonium ion solution used to obtain the data in the right-hand half of the above table is greater than that for the left so that the amount of product formed could be increased to an observable level. Here it can be seen that for those substituents which might reasonably be expected to be expelled easily (i.e. X = H, COO^-, and SO_3^-) there is no appreciable variation in yield, whereas for the other substituents the yield appears to be proportional to the coupler concentration. Again, in these cases of low yield the signal/noise ratio

was low and so these values (and hence this variation) should not be relied upon too heavily. It is probably not too unwise to say that there is essentially no variation in yield with coupler concentration for any of these compounds.

5.5 Summary

From the kinetic study it would seem that the base involved in removing the so-called 'electrofugal' leaving groups (X) from the Wheland intermediates is actually a second molecule of the coupling component involved in the reaction. From the analysis of the ipso-coupled-dye yields the following sequence of leaving abilities is proposed:

$$H \backsim COO^{\ominus} > SO_3^{\ominus} > CHO > CO\text{-}C_6H_4\text{-}NMe_2 > COCH_3 > CH_3$$

It is likely that this will apply only under the conditions used in the present study since the leaving ability of a particular group relative to another can be markedly affected by the conditions. As mentioned earlier, Fischer and Zollinger[18] found that the rate of substitution of bromine in 1-bromo-2-naphthol-6-sulphonic acid is increased by thio-sulphate but this effect was not observed for X = Cl or I.

It would seem, also from the yield studies, that the 4-methyl coupling component is actually undergoing substitution in the ortho-position rather than ipso-substitution. This supposition is based on the fact that alkyl groups generally are poor leaving groups and also that the bright red colour formed during the reaction strongly suggests the presence of an azo-dye. The second peak observed in the chromatogram

of the reaction mixture could be due to the N-coupled (N-demethylated) compound or, perhaps more likely in view of the intense red colour, the 2,6-diazo-dye.

When considering the results presented in this chapter it is important to bear in mind the fact that it is difficult to draw firm conclusions from rate measurements where the yield is very small since the measured rate constants will be a sum of rate constants including those of various side reactions.

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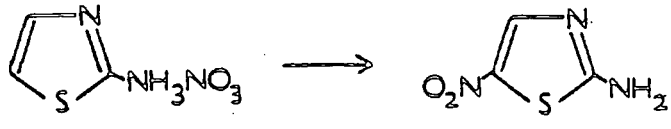
CHAPTER 6

EXPERIMENTAL DETAILS

6.1 Preparation and Purification of Materials.

The inorganic compounds used in this work were all 'AnalaR' grade and were used without further purification. Perchloric acid solutions were made up using CPR grade $HClO_4$ (60-62%) and then standardised by titration with standard sodium hydroxide solution using phenolphthalein indicator. Distilled water was used throughout and fresh sodium nitrite solutions were made up on the day of use. The aniline derivatives considered in chapters 1 and 2 were obtained commercially and recrystallised from aqueous ethanol before use. 3-Amino-1,2,4-triazole was obtained from ICI Organics Division, Blackley, Manchester, and was recrystallised before use. 2-Amino-thiazole nitrate was obtained from the same source and was used to prepare a sample of 2-amino-5-nitrothiazole as described below.

6.2 Preparation of 2-Amino-5-nitrothiazole.[1]



I II

2-Aminothiazole nitrate (40.75g, 91.3% pure, 0.23 mole) was added portionwise to cold (10°C) sulphuric acid (98%, 75cm^3). This was stirred for one hour and then allowed to attain room temperature, stirring for a further 18 hours (convenience). The mixture was then poured into 1.5 litres of ice/water, stirred for two hours, and then filtered at the pump (the insoluble material obtained was crude nitramine). The filtrate was neutralised with anhydrous Na_2CO_3 and

filtered at the pump. The solid obtained was then reslurried with ice/water and filtered off. This was dried at 120°C overnight. Yellow powder, yield 24.3g (79.8%). Melting point 196-198°C (decomp).

$C_3H_3N_3O_2S$ (II)	requires :	C	24.8%,	H	2.1%,	N 29.0%
	found :		24.5%,		1.7%	28.9%

6.3 Kinetic Measurements

All rate measurements were carried out at 25°C in either a conventional recording UV/VIS spectrophotometer or a stopped-flow instrument, as described below. The optimum analytical wavelength for each reaction was determined by obtaining spectra of reactant and product solutions and noting the wavelengths at which absorbance changes occurred. Reactions were monitored at constant wavelength by following the change in absorbance due to increasing product concentration (ArN_2^+) or diminishing reactant. These wavelengths are summarised below.

Amine	λ/nm	following:
2,4-dinitroaniline	410	decreasing [amine]
4-nitroaniline	245	increasing [product]
sulphanilamide	310	decreasing [HNO_2]
sulphanilic acid	300	" "
2-amino-5-nitrothiazole	405	decreasing [amine]
3-amino-1,2,4-triazole	280	increasing [product]

Since the UV/VIS absorbance (A) of a compound in solution is proportional to its concentration (c), a method of determining the observed first-order rate constant k_o is provided by the Beer-Lambert law, $A = \varepsilon c l$, where ε is the molar decaidic absorptivity ('extinction coefficient') and l is the path length (=1cm).

Consider the first-order reaction $R \longrightarrow P$. At time = t the concentration of P is given by

$$[P]_t = [R]_o - [R]_t$$

where $[R]_o$ is the initial concentration of R. Also, at $t = \infty$, we have

$$[R]_\infty = [P]_o = 0$$

and $$[P]_\infty = [R]_o$$

therefore $$A_o = \varepsilon_R [R]_o \quad , \quad l = 1\text{cm}$$

$$A_t = \varepsilon_R [R]_t + \varepsilon_P [P]_t$$

$$= \varepsilon_R [R]_t + \varepsilon_P ([R]_o - [R]_t)$$

Now, since $$A_\infty = \varepsilon_P [P]_\infty$$

we have $$A_t - A_\infty = \varepsilon_R [R]_t + \varepsilon_P [P]_t - \varepsilon_P [P]_\infty$$

$$= \varepsilon_R [R]_t - \varepsilon_P ([P]_\infty - [P]_t)$$

$$= \varepsilon_R [R]_t - \varepsilon_P [R]_t$$

$$= (\varepsilon_R - \varepsilon_P)[R]_t$$

therefore $A_t - A_\infty = \varepsilon_R[R]_t - \varepsilon_P[R]_t$

$$[R]_t = \frac{(A_t - A_\infty)}{(\varepsilon_R - \varepsilon_P)}$$

Now, for a first-order reaction,

$$k_o = \frac{1}{t} \log_e \frac{[R]_o}{[R]_t}$$

$$k_o = \frac{1}{t} \log_e \frac{(A_o - A_\infty)}{(A_t - A_\infty)}$$

and hence:

$$\log_e(A_t - A_\infty) = -k_o t + \log_e(A_o - A_\infty) \qquad (6.1)$$

Thus a plot of $\log_e(A_t - A_\infty)$ vs t will be a straight line of slope $-k_o$. Values of A_t were measured at regular intervals over at least two half-lives and A_∞ was measured after 10 half-lives (>99% reaction). In some cases good values of A_∞ were not obtained (due to decomposition of ArN_2^+ etc.) and so the method of Guggenheim[2] was employed to evaluate k_o. Absorbance readings were taken at times $t_1, t_2, t_3, \ldots$ and also at $t_1 + \Delta, t_2 + \Delta, t_3 + \Delta, \ldots$ where Δ is at least one (preferably two) half-lives. If A_n is the absorbance measured at time t_n and A'_n is that at time $t_n + \Delta$, then for a first-order reaction:

$$(A_n - A_\infty) = (A_o - A_\infty) e^{-k_o t_n} \qquad (6.2)$$

$$(A'_n - A_\infty) = (A_o - A_\infty) e^{-k_o (t_n + \Delta)} \qquad (6.3)$$

where

$$\frac{(A_n - A_\infty)}{(\varepsilon_R - \varepsilon_p)} = [R]_t$$

and

$$\frac{(A_o - A_\infty)}{(\varepsilon_R - \varepsilon_p)} = [R]_o \quad , \text{ as before}$$

Subtracting 6.3 from 6.2 :

$$(A_n - A'_n) = (A_o - A_\infty) e^{-k_o t_n} (1 - e^{-k_o \Delta})$$

therefore,

$$\log_e (A_n - A'_n) = -k_o t_n + \log_e ((A_o - A_\infty)(1 - e^{-k_o \Delta}))$$

. . . . . (6.4)

and a plot of $\log_e (A_n - A'_n)$ vs t_n will result in a straight line of slope $-k_o$. In deriving these equations is assumed that the decrease in absorbance due to reactant is being followed (i.e. $A_\infty < A_t$ in 6.1, and $A'_n < A_n$ in 6.4). For reactions followed by

monitoring the increase in absorbance due to product it is easy to show that the corresponding equations are:

$$\log_e (A_\infty - A_t) = -k_o t + \log_e (A_\infty - A_o)$$

and

$$\log_e (A'_n - A_n) = -k_o t_n + \log_e ((A_\infty - A_o)(1 - e^{k_o \Delta}))$$

All four possibilities (i.e. normal and Guggenheim methods, increasing and decreasing absorbance measurements) can be conveniently represented by the following forms:

$$\log_e \left| A_\infty - A_t \right| = -k_o t + \text{constant} \qquad \text{(Normal)}$$

$$\log_e \left| A'_n - A_n \right| = -k_o t_n + \text{constant} \qquad \text{(Guggenheim)}$$

A method similar to that of Guggenheim was developed by Swinbourne[3] for which the following equation was derived. Dividing 6.2 by 6.3 gives:

$$A_n = A'_n e^{k_o \Delta} + A_\infty (1 - e^{k_o \Delta})$$

or:

$$A_n = A'_n e^{k_o \Delta} + \text{constant}$$

This equation is independent of t and is the same for increasing and decreasing absorbance values. A plot of A_n vs A'_n will result

in a straight line of slope $e^{k_o\Delta}$. This method is simpler than the Guggenheim method since A_n and A'_n values can be plotted directly, avoiding the need to calculate values of $\log_e |A'_n - A_n|$.

6.4 Instrumentation.

Reactions were followed at constant wavelength by monitoring the change in absorbance due to a reactant or product, as already stated. Two types of instruments were used for this: conventional recording UV/VIS spectrophotometers (for reactions with half-lives greater than about 10 seconds), or a stopped-flow instrument ($t_{\frac{1}{2}} < 10s$). With both methods rate constants were determined 3 to 5 times and an average taken.

6.4.1 Recording UV/VIS Spectrophotometers.

Two of these instruments were available. These were a Beckmann model 25 spectrophotometer and a Pye-Unicam SP8-100 instrument. All reactions were carried out at 25°C, maintained by electrical thermostatting of the cell compartment (Beckmann) or by circulating thermostatted water (Pye-Unicam). Flasks containing reactant solutions were immersed in a thermostatted water bath before use. Both were double beam instruments and distilled water was used as reference in all cases.

Two solutions were prepared for each reaction using distilled water as solvent. One contained sodium nitrite, the other contained the amine and perchloric acid, plus a nucleophile (Cl^-, Br^-,... etc.) where nucleophile catalysis was to be studied. 1ml samples of each

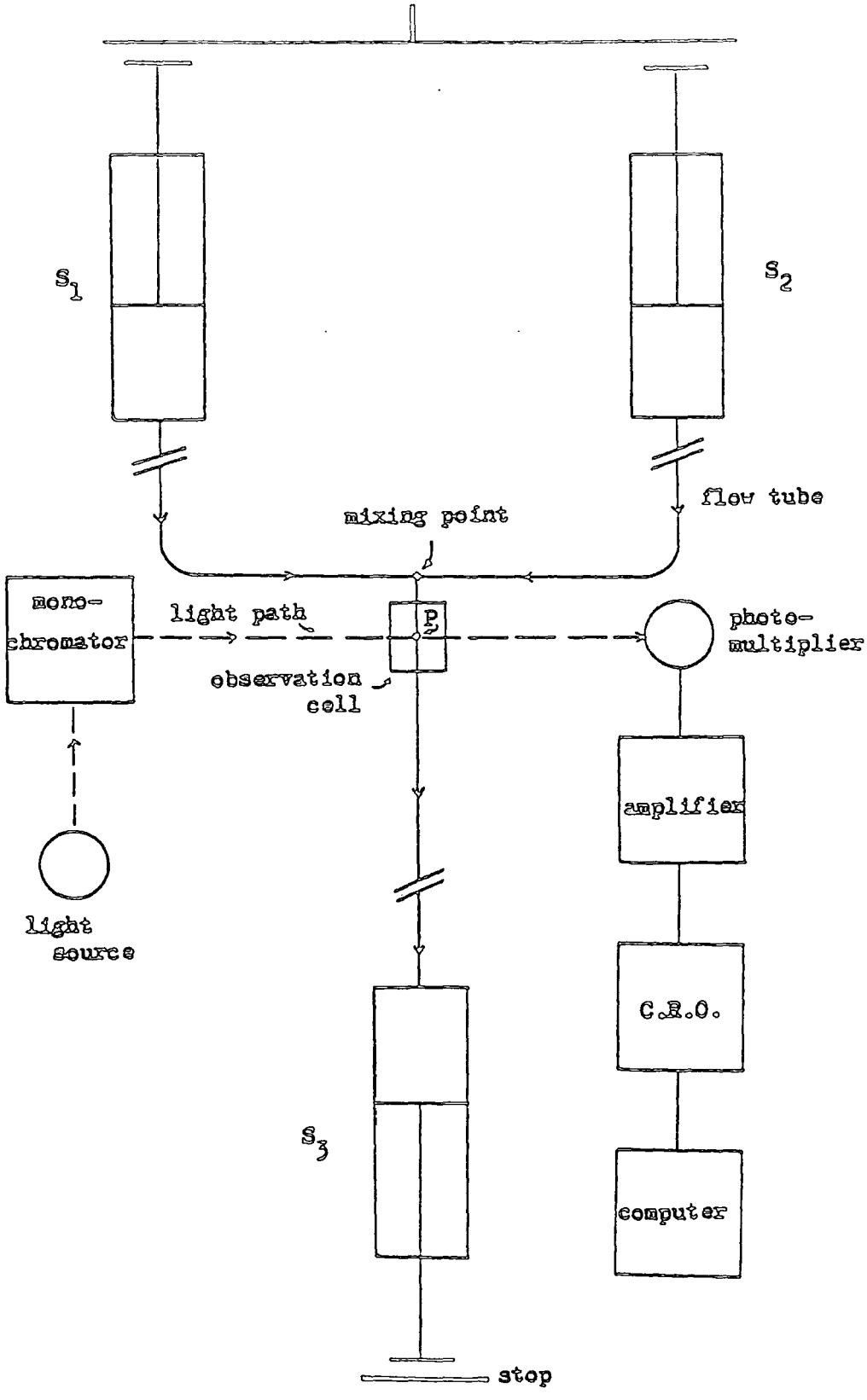
were mixed rapidly in a 2ml silica cell (thus halving the concentrations) and immediately placed in the sample cell holder of the spectrophotometer. The reaction was then monitored at the appropriate wavelength. A 'hard copy' of the absorbance vs time trace was obtained and used to determine absorbance values at fixed time intervals and also A_∞. These values were then used as input data for a computer program which evaluates first-order rate constants. For Guggenheim and Swinbourne plots values of A'_n and $t_n + \Delta$, and A_n and A'_n respectively were used as input for a graph plotting program. In all cases Apple computers were used (II Europlus and IIe) with 'in-house' generated software.

6.4.2 Stopped-Flow Spectrophotometer.

For reactions with half-lives shorter than about 10 seconds the use of stopped-flow instrumentation is required. In the present work a Hi-Tech instrument was used and this was interfaced with an Apple II Europlus microcomputer using Hi-Tech stopped-flow data acquisition software. The set-up is shown in the diagram on the following page.

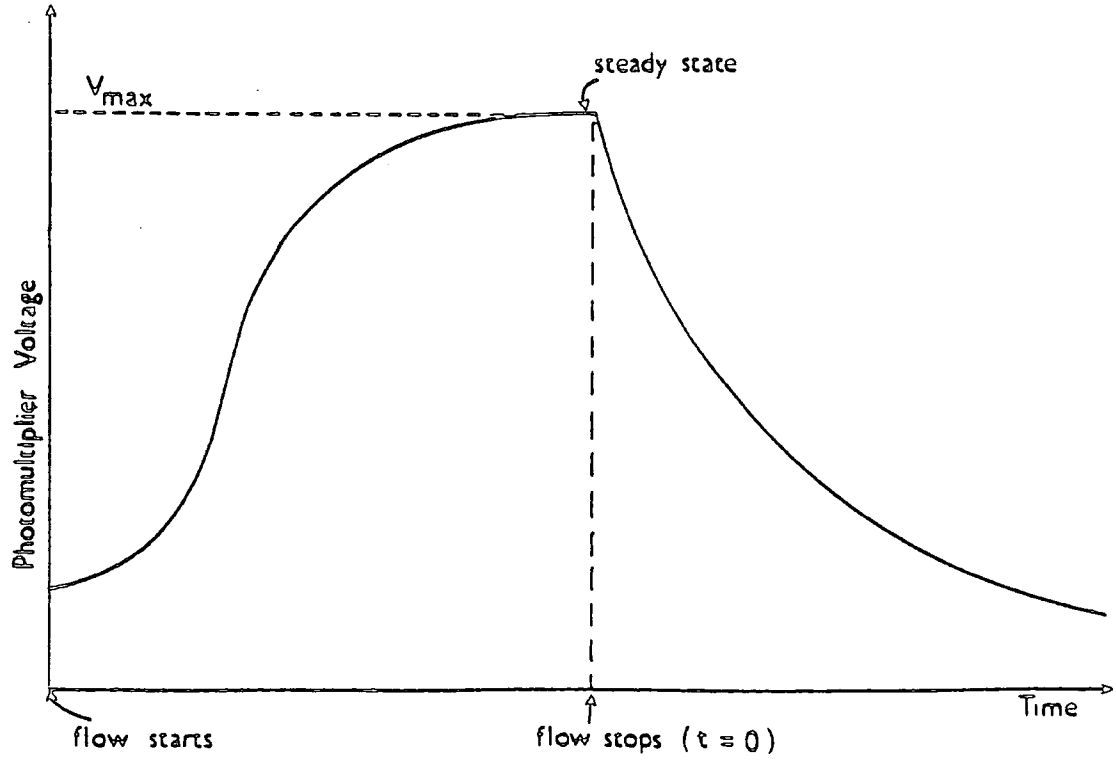
The two reactant solutions (prepared as described above) were placed in seperate syringes S_1 and S_2. When the pistons are pushed simultaneously (by another piston, driven pneumatically) the reactants move along the flow tubes with identical velocities and past the mixing point where the concentrations are halved and the reaction begins. The mixed solution, in which the reaction is now proceeding, then enters a third syringe, S_3. This forces the piston of S_3 out

STOPPED-FLOW SET-UP.



until it reaches a stop, when the flow suddenly halts and the oscilloscope trace is triggered. A beam of monochromatic light (of the required wavelength) is passed through the solution at the point P (2mm path length) and its intensity is converted into a proportional electrical signal which is then displayed on the storage oscilloscope. Absorbance values are then read off the trace and used as input data for the computer program, as in section 6.4.1. For very fast reactions (complete in less than 5sec.) the data acquisition software allows direct sampling of the photomultiplier signal voltage by the computer.

The variation of signal voltage with time (at the point P) is shown in the diagram below.



The corresponding plot of absorbance vs time would be similar in shape but inverted, since signal voltage is inversely proportional to absorbance. The above diagram, therefore, represents a reaction in which an increase in absorbance is being measured. Initially the voltage is at a minimum (maximum absorbance due to product), a condition achieved by first flushing the apparatus through with reactant solutions. After the flow begins the voltage increases (as the concentration of the absorbing species at the observation point decreases) until it reaches a maximum steady-state value. This maximum does not represent the situation in which [product] = 0, since in the time taken for the solution to move from the mixing point to the observation point some reaction will have occurred and a small amount of product formed. This so-called 'dead time', although very short, sets an upper limit for measurable reaction velocities using this method. If a substantial proportion of the reaction takes place during this time then an alternative technique must be sought. None of the reactions studied in the present work were fast enough for this to be a problem. The steady-state condition is maintained for a short time until the flow stops, when the major part of the reaction commences and the oscilloscope trace is triggerred. The whole process, from flow-start to flow-stop, takes place in less than a second. Again, reactions were studied at 25°C, maintained by immersion of the flow-tubes in an electrically thermostatted ethylene glycol solution (necessary because the instrument can be used at temperatures below 0°C).

6.5 Typical Kinetic Run

An example of a kinetic run is given in the table below. This is for the acid catalysed diazotisation of 2-amino-5-nitrothiazole.

time/s	Abs.
12	0.542
24	0.501
36	0.469
48	0.441
60	0.418
72	0.399
84	0.382
96	0.362
108	0.358
120	0.349

$A_{\infty} = 0.311$ $\quad k_o = 0.01339\ s^{-1}$

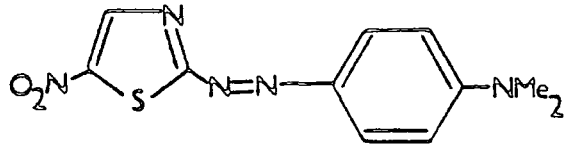
A typical set of duplicate runs is shown below for the same reaction.

Run	k_o/s^{-1}
1	0.01306
2	0.01385
3	0.01338
4	0.01368
5	0.01339

$k_o = 0.0134 \pm 2.7 \times 10^{-4}\ s^{-1}$

6.6 Preparation of Thiazole Dye[4].

In order to detect the presence of the diazonium ion derived from 2-amino-5-nitrothiazole the reaction mixture was added to a buffered (pH 8) solution of N,N-dimethylaniline and a UV/VIS spectrum obtained. The spectrum contained absorptions identical to those in the spectrum of the dye prepared as follows.



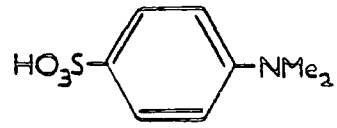
Sodium nitrite (2.2g, 0.032 mole) was dissolved in hot (70°C) sulphuric acid (15ml) and the mixture cooled below room temperature. A mixture of propionic and acetic acids (30ml) in the ratio 1:5 was added, maintaining the temperature below 20°C. The mixture was then cooled to below 5°C and 2-amino-5-nitrothiazole (4.35g, 0.03

mole) was added followed by a further portion of 1:5 acid (30ml). Diazotisation was allowed to continue for two hours maintaining the temperature below 5°C , and the resulting diazonium ion solution was added dropwise to a solution of 4-N,N-dimethylamino-benzoic acid in dilute sulphuric acid (for the chemistry involved see chapter 5). The dye was precipitated immediately and was filtered off and washed with water. Thin layer chromatography showed the dye to be in a very pure state.

6.7 Experimental Details for Chapter 5.

Of the compounds used in this study, the inorganic compounds were AnalaR grade, available commercially; N,N-dimethylaniline was obtained commercially; and the other coupling components were obtained from the Fine Chemicals service of ICI Organics Division, Blackley, Manchester, with the exception of 4-N,N-dimethylamino-benzenesulphonic acid, which was prepared as follows.

6.7.1 Preparation of 4-N,N-dimethylaminobenzenesulphonic acid[5].

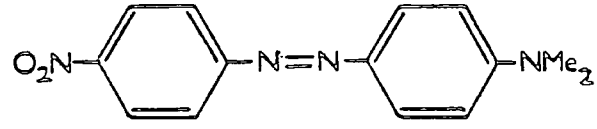


N,N-dimethylaniline (60.5g, 63.3ml, 0.5mole) was dissolved in tetrachloroethane (80ml) and this was then added dropwise to a stirred solution of chlorosulphonic acid (58g, 35ml). During the addition the temperature was maintained below 30°C using an ice/water bath. After the addition the mixture was stirred for an hour and then

refluxed at 180°C (oil bath). After about 45mins. an off-white solid precipitated. This was then allowed to cool and stand overnight. The solid was then filtered off and washed with tetrachloroethane and 40/60 petroleum ether. The addition of acetone to a hot aqueous solution of this solid precipitated fine white crystals, m.pt. 266-268°C (decomp).

$C_8H_{11}NSO_3$	requires :	C	47.8%,	H	5.5%	N 7.0%
	found :		47.5%		5.6%	6.7%

6.7.2 Preparation of 4-N,N-dimethylamino-4'-nitroazobenzene[6].



4-Nitroaniline (21g, 0.15mole) was dissolved by warming with 50ml of concentrated hydrochloric acid in 50ml of water. 200ml of water was added and the solution cooled to 0-5°C by adding 200g of ice. This caused some precipitation of 4-nitroaniline but the preparation was continued with some solid present. Sodium nitrite (80ml of a 0.2M solution) was added quickly and the mixture stirred and filtered to remove diazo-decomposition products. N,N-dimethylaniline (18.2g, 0.16mole) was added to the filtrate and the mixture stirred for about 2 hours. The red solid was then filtered off and dissolved in acetone. This was then filtered and water added, resulting in precipitation of the dye. The mixture was cooled in an

ice bath and filtered. Amorphous red solid.

$C_{14}H_{14}N_4O_2$	requires :	C	62.2%	H	5.2%	N 20.7%
	found :		62.6%		4.8%	19.7%

This compound was used to prepare a standard curve (integration vs concentration) by HPLC in order to determine product yields from the ipso-coupling reactions, since it is the expected common product of each reaction.

6.7.3 Kinetic Method and Reaction Conditions.

Reactions were carried out by first preparing a solution of diazotised 4-nitroaniline and reacting this with a buffered solution of the coupling component. $1cm^3$ of 0.02 M 4-nitroaniline solution ($[H^+]$ = 0.2M) was mixed with $2cm^3$ of 0.04M sodium nitrite in a $100cm^3$ volumetric flask. This was allowed to react for 15mins. before dilution to $100cm^3$ with 50% aqueous acetone. A $25cm^3$ aliquot of this was then diluted to $100cm^3$ to yield a 10^{-4}M diazonium ion solution. In practise, slight variations on this method were necessary as fresh solutions were needed.

Reactionswere carried out using a stopped-flow instrument (as described earlier) in the wavelength range 500-600nm following the increase in absorbance due to the bright red dye. The only exception to this was the reaction of 4-formyl-N,N-dimethylaniline (X = -CHO), which required the use of a recording instrument at 500nm with a higher concentration of diazonium ion solution (in order to increase

[product] to an observable level). As before, concentrations are halved on mixing equal volumes of reactant solutions.

The virtual insolubility of the dye in water necessitated the use of 50% aqueous acetone as solvent. Under these conditions a lower proportion of acetone resulted in precipitation of the dye. Coupler solutions were prepared in a standard phosphate buffer (measured pH = 7.9) comprising KH_2PO_4 and Na_2HPO_4 (0.025M in each, 50% aqueous acetone solvent) and reactions carried out under first-order conditions ([coupler] $\gg$ [diazo]). The five-or-so individual kinetic runs required to provide a good average rate constant were carried out using the same diazonium ion solution. On average five runs took less than 15mins. to carry out and so the diazonium ion solution was never more than about 30mins. old. No appreciable decomposition was observed over this period when the solution was monitored in a recording spectrophotometer. Again, the only exception to this was the 4-formyl coupler. In this case fresh diazonium ion solutions were prepared for each individual kinetic run, since five repeats would have taken about 90mins. In all cases the pH of the reaction mixture was checked and always fell into the range 7.85-7.92. For the 4-carboxylate and 4-sulphonate couplers it was necessary to adjust the pH of the coupler solution by the addition of a small amount of anhydrous sodium carbonate. During preliminary work to determine a useful pH for the study of these reactions it was noticed that acidification of a borate-buffered reaction solution (pH 10) resulted in the disappearance of the bright red colouration originally attributed to the dye. This occurred even when the reaction

mixture was allowed to stand overnight and acidified the next day. This red compound may have been diazohydroxide, acidification of which would result in regeneration of the diazonium ion and hence loss of colour. On acidification of the phosphate-buffered reaction mixtures the red colouration remained and so complications due to formation of unreactive diazohydroxide can be ruled out.

6.7.4 Determination of Dye ε_{max}.

It was originally intended to determine the dye yields from these reactions using a scanning UV/VIS spectrophotometer and measuring absorbance values from the spectra. This requires the knowledge of the extinction coefficient (ε_{max}, c.f. Beer-Lambert law). The details of the determination of ε_{max} are presented here, although yields were later measured by the more accurate method of HPLC (see section 6.7.7).

Consider the Beer-Lambert law: $A = \varepsilon c l$, where A = absorbance, ε = extinction coefficient, c = concentration, and l = path length = 1cm. A plot of A vs c will result in a straight line of slope ε. Absorbance values were measured at four concentrations of dye in 50% aqueous acetone at the absorption maximum of 493nm. Each individual absorbance value in the table below is an average of three seperate determinations. From the slope of the graph ε_{max} = 38250. ($\log_{10} \varepsilon_{max}$ = 4.58).

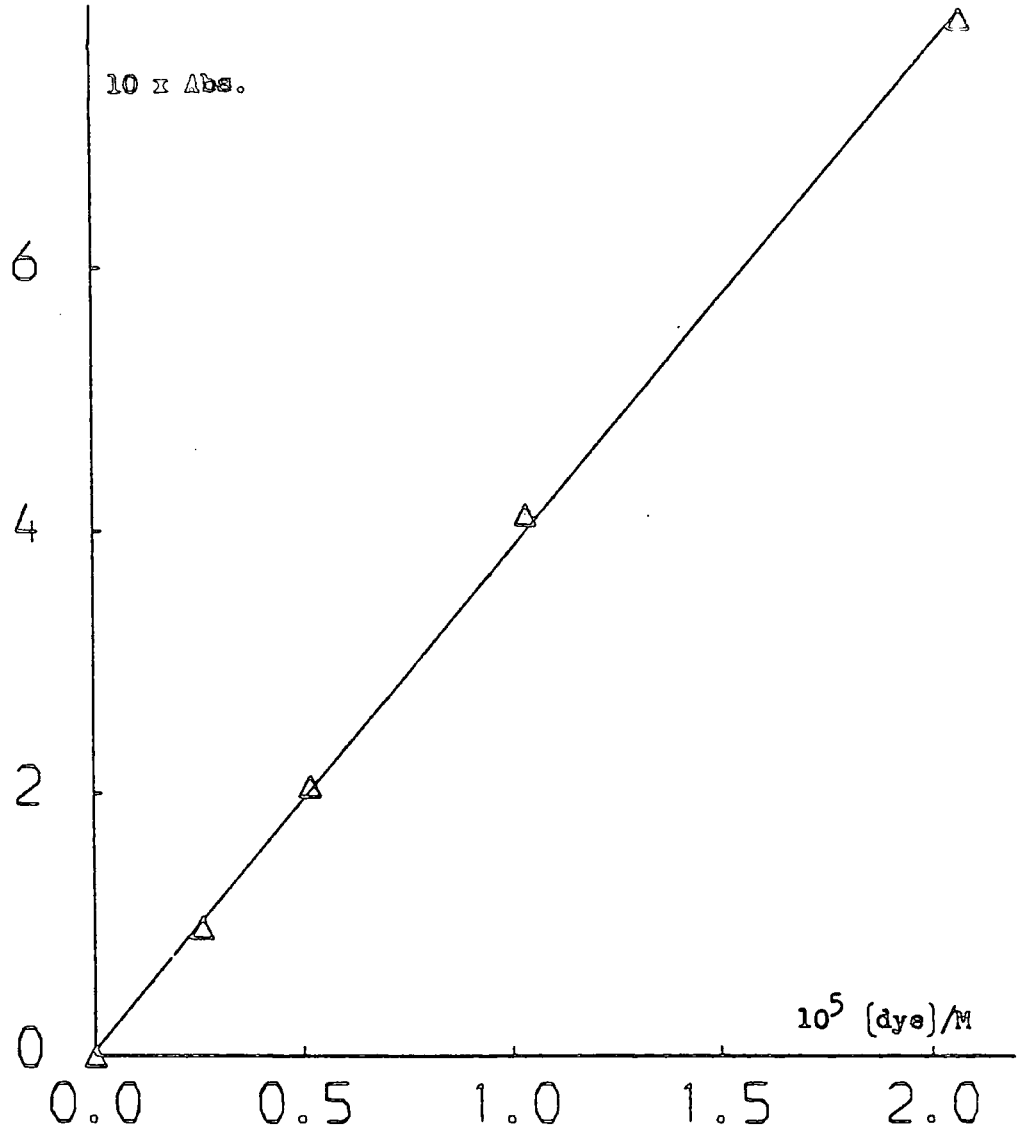


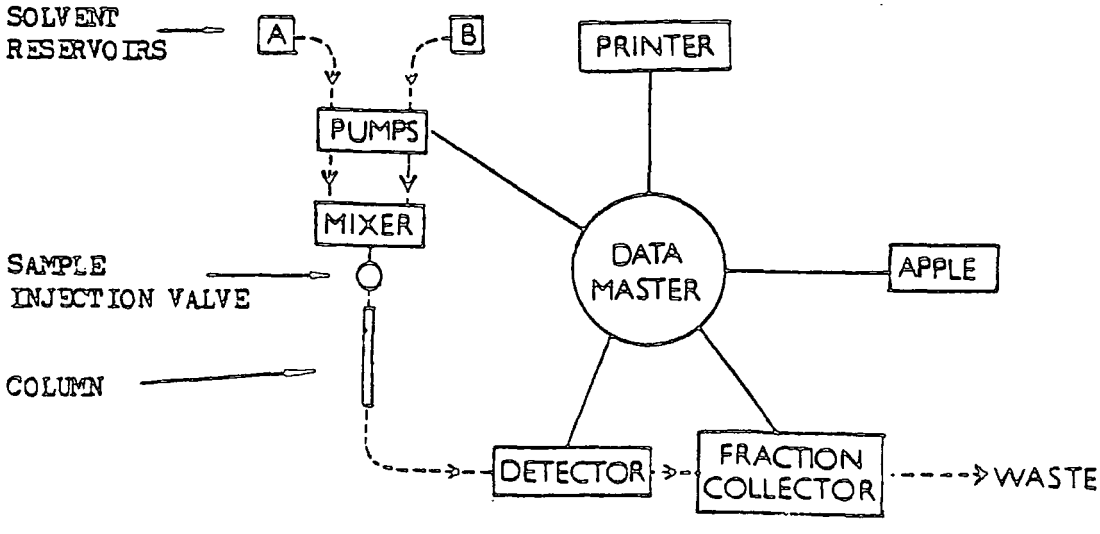
FIG. 6.1 — Determination of Dye ε_{max}

DETERMINATION OF DYE ε_{max}-

10^6 x [dye]/M	Abs.
0	0
2.59	0.0978
5.19	0.206
10.4	0.413
20.7	0.791

6.7.5 High Performance Liquid Chromatography (HPLC).

This section describes the hardware used in the determination of coupling reaction yields, and the general 'housekeeping' required for the system to function properly. Below is a diagrammatic representation of the set-up, where solid lines represent electrical communication and broken lines represent solvent flow.



The main component of the system is the Data Master which controls the various peripherals, i.e. pumps, fraction collector, and printer. The components of the system are itemised below, giving details of their specific function.

a) SOLVENT

Generally, aqueous-organic solvents are used for reverse-phase HPLC (i.e. polar mobile phase, non-polar stationary phase). The organic solvent chosen for the present work was acetone, since this was used as the reaction solvent and avoids the possibility of a solvent peak in the chromatogram. The two solvents (water and acetone) are stored in seperate reservoirs and drawn up by seperate pumps. The two solvent streams then pass through a mixer and emerge as a homogeneous mixed solvent which then continues through the injection valve, where the sample is introduced, and onto the column. It is vital that the solvents used in HPLC generally are of very high purity and free from particulate matter which may damage pump seals and valves. For this reason water is double-distilled and organic solvents are filtered using a membrane filter. HPLC grade solvents are recommended as these are free from trace organic impurities which may affect peak areas at short wavelengths. However, AnalaR grade acetone was found to be satisfactory at the longer wavelengths used in the present work. Solvents must be degassed to avoid post-column (i.e. pre-detector) degassing, which occurs when the pressurised solvent (~2000psi) emerges from the column into the flow tubes to the detector (atmospheric pressure).

b) PUMPS

The present work utilises the technique of Gradient Elution HPLC, i.e. liquid chromatography in which the solvent composition (in this case the water/acetone ratio) is varied during the run. This is achieved, maintaining a constant flow rate of $1cm^3$/minute, by varying the pumping rate of each pump (controlled electronically by the Data Master). For example, a solvent ratio of 1:1 would require each pump to operate at a flow rate of $0.5cm^3$/min. (total flow rate $1cm^3$/min.), whereas for 100% acetone the acetone pump would operate at $1cm^3$/min. and the water pump would be idle (vice-versa for 100% water). In between these extremes the solvent composition can be varied almost continuously. This gradient elution is extremely useful as it allows the relative retention times of several peaks in the chromatogram to be altered (since retention time depends upon solvent composition, amongst other factors) allowing a good seperation to be achieved by appropriate choice of gradient. The gradient profile is input to the Data Master via an Apple IIe computer, which acts as the operator's interface with the system and allows the alteration of various parameters such as run time, flow-rate, etc. A typical chromatogram is shown on the following page, with the gradient profile indicated. A gradient was used in this case to reduce the retention time of the dye, thus allowing a more rapid throughput of samples.

c) SAMPLES

As with solvents, samples must be filtered prior to injection to remove potentially damaging particulate matter, and also the sample

Sequence #: 2
Inject time:11: 5:43 Date: 7/23/85
File:DMA.A002

Operator:JF
Method:AZO
Detector:493nm 0.5AUFS
Column:ZORBAX ODS
Flow:1ML/MIN
Mobile Phase:ACETONE/WATER
Inject amt.:100ul

DIMETHYL ANILINE
493nm DYE ABS. MAX.

Run time: 20.00
Peak width: 0.50
Peak sensitivity: 0.01
Min. area: 7000.

----Unknown Report

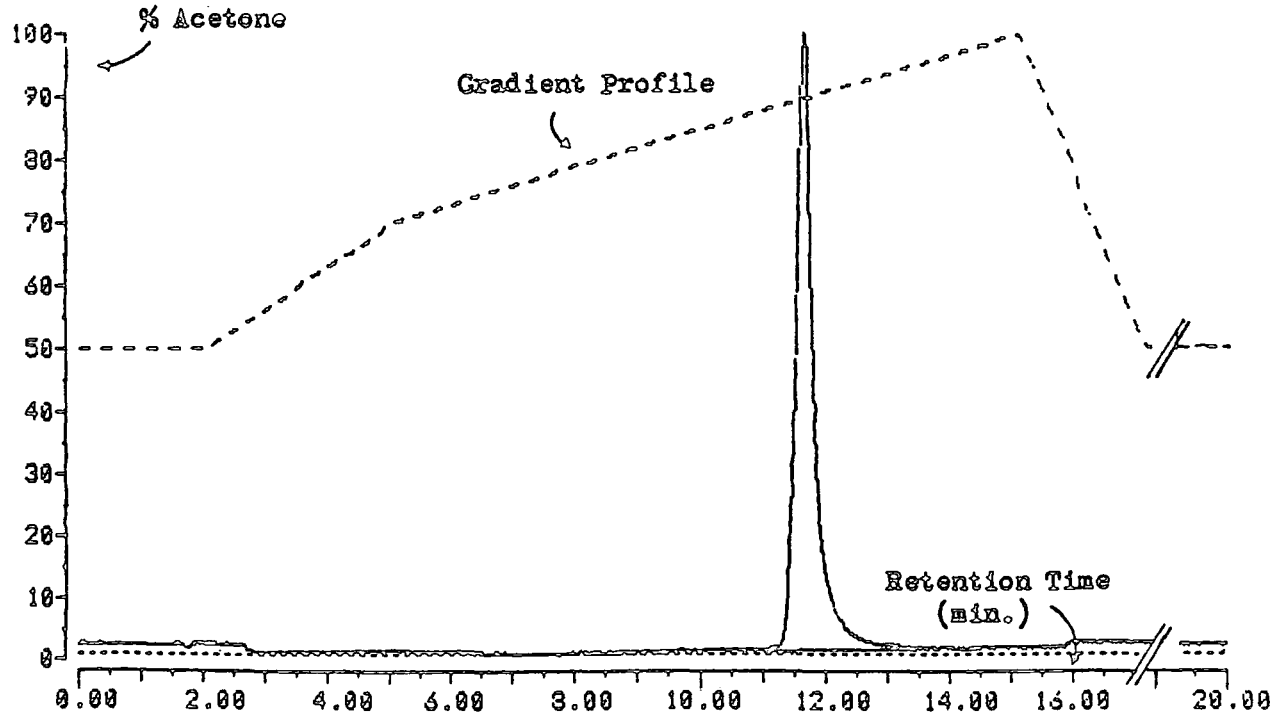
RT	Area	Area%	Label
11.66	235070.	100.000	AZO DYE

4 Peaks integrated

Diazotised 4-nitroaniline

+ dimethyl aniline

reaction product.



alysis channel A = 0.35 mV F. S.
ternate channel C = 10.00 mV F. S.

pH must be in the range 2-8 to avoid degradation of the column packing material. Injection volumes of 100µl were used in the present work. In practise, approximately $1cm^3$ of sample was loaded onto a 100µl loop (a coiled metal tube which holds the sample), which then overflowed through a vent to waste. This ensured that the loop was completely filled with sample and purged of any remaining solvent from the previous run. The loop was then connected to the solvent stream and the run started.

d) COLUMN

Reverse-phase chromatography involves the use of a polar mobile phase (solvent) and a non-polar stationary phase (adsorbent packing material). In the present work a 15cm column packed with Zorbax ODS (Octadecyl silane) was used. This retains the dye until the solvent composition is about 80:20 acetone:water (see chromatogram, previous page). In normal-phase chromatography a non-polar solvent is used (e.g. methanol/hexane) and a polar stationary phase (silica).

e) DETECTOR and DATA MASTER

The detector was a normal variable wavelength UV/VIS source-detector-photomultiplier set-up. The electrical output from this was monitored by the Data Master and relayed to a printer, which produced a chromatogram similar in form to that from a conventional recorder-coupled system. When the set run-time had elapsed the Data Master then generated a report which listed the various parameters used etc. and included a scaled plot of the chromatogram. The chromatogram on the previous page is a typical example of a report of this type.

6.7.6 Dye Calibration Runs.

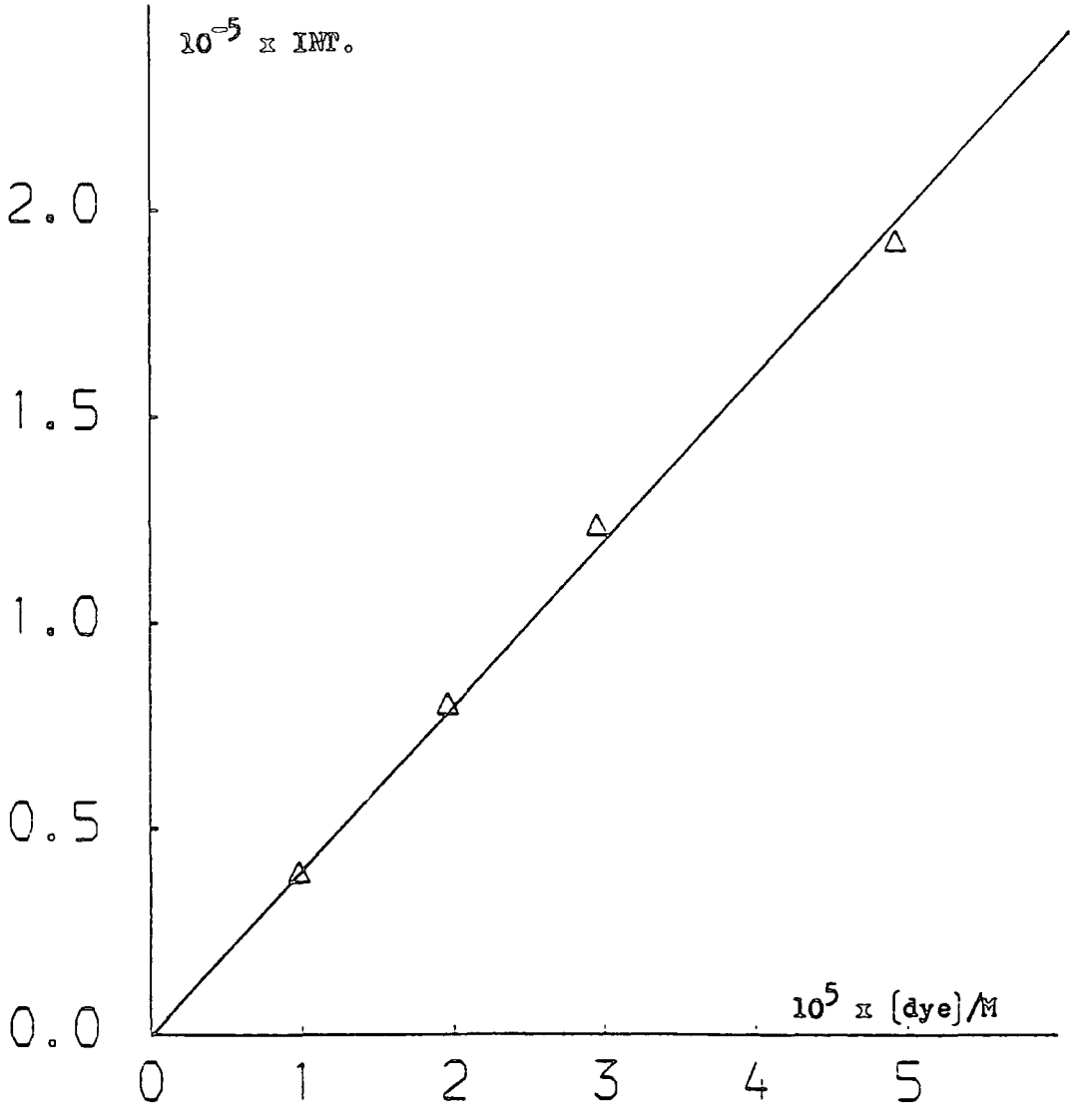
In order to measure the coupling reaction yields it was necessary to prepare a standard curve (peak integration vs dye concentration) using the dye synthesised as in section 6.7.2. This involved simply preparing solutions (in 50% aqueous acetone) of different concentrations and obtaining chromatograms. 100µl samples of each solution were injected in triplicate to obtain average peak integration values. The integration values obtained and the corresponding concentrations are shown in the following table and the graph is shown on the following page.

10^5 x [dye]/M	10^{-4} x INT.
0	0
0.982	3.96
1.96	8.06
2.95	12.4
4.91	19.3

SLOPE = $3.93 \times 10^{9} M^{-1}$

6.7.7 Yield Measurements.

Reactant solutions were prepared as described in section 6.7.3. Reactions were carried out by mixing equal volumes, usually $1cm^3$ + $1cm^3$,



HPLC Dye Calibration

in a $10cm^3$ volumetric flask and then diluting to the mark. Those reactions with low yields (faint colour formation) were not diluted. Each run was carried out three times and for this purpose three reaction solutions were prepared using the same diazonium ion solution. These were injected (100µl) onto the column to produce the chromatograms from which an average peak integration value was obtained. The dye concentration in the diluted solution was then determined using the standard curve described above, and the dye yield from the reaction was then calculated using this. Coupler concentrations were varied ([coupler] = X, X/2, X/4) to determine the effect of this on the yield. The results are presented in chapter 5, page 152.

6.8 Treatment of Errors.

In the preceding chapters errors in rate constants are reported as standard deviations from the mean of at least three (usually five) individual kinetic runs. For a finite number, n, of observations, X, the sample standard deviation is defined by:

$$\sigma = \sqrt{\left(\frac{\sum(X - \bar{X})^2}{(n - 1)}\right)}$$

where $\bar{X}$ is the mean value of all observations.

6.8.1 Method of Least Squares[7].

In correlating the mean rate constant values with the corresponding independent variables (i.e. [amine], $[H^+]$, $[X^-]$, ...etc.)

the method of least squares linear regression analysis has been used in these cases where it is appropriate.

The object of the method is to obtain the optimum values of α and β in the equation $y_i = \alpha + \beta x_i$, where in this case y_i is synonymous with k_o and x_i with the independent variable. In other words, we wish to fit the 'best' straight line to the data, where α is the intercept and β is the slope of the line. The regression line is regarded as having the best fit to the data when the values of α and β are chosen to minimise the sum of the squares of the deviations of the points (x_i , y_i) from the line:

$$S = \sum_{i=1}^{m} (y_i - \alpha - \beta x_i)^2$$

For S to be a minimum $\delta S/\delta\alpha = \delta S/\delta\beta = 0$ and, replacing α and β by their estimates a and b we have:

$$\sum (y - a - bx) = 0$$

and

$$\sum x(y - a - bx) = 0$$

The subscripts i are dropped since the summations are assumed to be over all m observations. Rearrangement of these gives the simultaneous equations:

$$\sum y = ma + b\sum x \qquad (6.5)$$

and

$$\sum xy = b\sum x^2 + a\sum x$$

and hence:

$$b = \frac{n\sum xy - \sum x \sum y}{n\sum x^2 - (\sum x)^2} \quad = \text{'best' slope}$$

from (6.5):

$$a = \frac{\sum y - b\sum x}{n}$$

$$= \bar{y} - b\bar{x}$$

where $\bar{y}$ and $\bar{x}$ are mean values.

For those plots which pass through the origin we minimise

$$S = \sum_{i=1}^{n} (y_i - bx_i)^2$$

and hence:

$$\sum x(y - bx) = 0$$

$$\sum xy - b\sum x^2 = 0$$

$$b = \frac{\sum xy}{\sum x^2} \quad = \text{'best' slope}$$

For a linear transformation involving the reciprocal form of a rate equation this method is unsatisfactory because of distortion

of the error span due to reciprocation and the bias this places on points at higher values of $1/(k'_o)$. To overcome this problem weighted least squares linear regression analysis is used.

6.8.2 Weighted Least Squares Linear Regression Analysis[8].

Taking reciprocals of experimentally determined - and error prone - data causes distortion which can lead to erroneous slope and intercept values but which can be overcome by suitably weighting the regression line. The optimum regression line is thus the one that minimises the weighted sum of the squares of the deviations:

$$S = \sum_{i=1}^{m} w_i (y_i - \alpha - \beta x_i)^2$$

The normal equations, in terms of a and b, are now:

$$a\sum w + b\sum wx = \sum wy$$

$$a\sum wx + b\sum wx^2 = \sum wxy$$

which can be solved for a and b to give:

$$b = \frac{\sum w . \sum wxy - \sum wy . \sum wx}{\sum w . \sum wx^2 - (\sum wx)^2}$$

$$a = \frac{\sum wy}{\sum w} - b\frac{\sum wx}{\sum w} = \bar{y} - b\bar{x}$$

The most efficient statistical weighting factor, in the case of a linear transformation of the type carried out in the present work, is given by:

$$w_i = \frac{v_i^4}{\sigma_{v_i}^2}$$

where $\sigma_{v_i}^2$ is the variance of the original velocity v_i determined at a substrate concentration $[s_i]$. The weighting factor indicates that the double-reciprocal plot is increasingly weighted as the velocity increases (i.e. at low $1/[s]$), thus offsetting the bias in the unweighted linear regression at low values of v (i.e. at high $1/[s]$).

When using this method it must be borne in mind that any point with a large error will weight the curve unduly in its favour. Using a computer program - a FORTRAN listing of which (taken from reference 8) was translated into BASIC for the purposes of the present work - weighted least squares linear regression analysis was carried out, after which the 'worst' point (i.e. that with the largest error) was removed and the remaining data reprocessed. This cycle was repeated, each time removing the worst point (if necessary) from the remaining data until a Student t-Test showed no significant difference between the slope and intercept values calculated using n (say) points, and those calculated using $n - 1$ points (i.e. worst point removed). These optimum values were then reported.

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1) J.B. Dickey, E.B. Towne, & G.F. Wright, J. Org. Chem., 499, (1955)

2) E. Guggenheim, Phil. Mag., 2, 538, (1926)

3) E.S. Swinbourne, J. Chem. Soc., 2371, (1960)

4) L. Shuttleworth, British Patent No. 2036775

5) Experimental details furnished by ICI plc

6) H.E. Fierz-David, & L.B. Blangey, 'Fundamental Processes of Dye Chemistry', Interscience Inc., New York, (1949), p6

7) See for example C. Chatfield, 'Statistics for Technology', Chapman Hall Ltd., London, (1978)

8) D.V. Roberts, 'Enzyme Kinetics', Cambridge Univ. Press, Appendix II, (1977)

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APPENDIX

Appendix

Lectures and seminars organised by the Department of Chemistry during the period October 1982 - September 1985

(✧ denotes lectures attended)

13.10.82 Dr. W.J. Feast (Durham)
"Approaches to the Synthesis of Conjugated Polymers"

14.10.82 Prof. H. Suhr (Tubingen, West Germany)
"Preparative Chemistry in Non-Equilinrium Plasmas"

27.10.82 Dr. C.E. Housecroft (Oxford High School/Notre Dame)
"Bonding Capabilities of Butterfly-Shaped Fe_4 Units. Implications for C-H Bond Activation in Hydrocarbon Complexes"

28.10.82 ✧ Prof. M.F. Lappert, FRS (Sussex)
"Approaches to Asymmetric Synthesis and Catalysis using Electron-Rich Olefins and some of their Metal Complexes.

15.11.82 Dr. G. Bertrand (Toulouse, France)
"Curtius Rearrangement in Organometallic Series: A Route for New Hybridised Species"

24.11.82 Prof. F.R. Hartley (RMCS, Shrivenham)
"Supported Metal-Complex Hydroformylation Catalysts"

24.11.82 Prof. G.G. Roberts (Applied Physics, Durham)
"Langmuir-Blodgett Films : Solid-State Polymerisation of Diacetylenes"

08.12.82 Dr. G. Wooley (Trent)
"Bonds in Transition-Metal Cluster Compounds"

12.01.83 ✧ Dr. D.C. Sherrington (Strathclyde)
"Polymer-Supported Phase Transfer Catalysts"

09.02.83 ✧ Dr. P. Moore (Warwick)
"Mechanistic Studies in Solution by Stopped-Flow F.T-NMR and High-Pressure NMR Line Broadening"

21.02.83 Dr. R. Lynden-Bell (Cambridge)
"Molecular Motion in the Cubic Phase of NaCN"

02.03.83 Dr. D. Bloor (Queen Mary College, London)
"The Solid-State Chemistry of Diacetylene Monomers and Polymers"

08.03.83 Prof. D.C. Bradley, FRS (Queen Mary College, London)
"Recent Developments in Organo-Imido Transition-Metal Chemistry"

09.03.83 ✧ Dr. D.M.J. Lilley (Dundee)
"DNA, Sequence, Symmetry, Structure, and Supercooling"

11.03.83 Prof. H.G. Viehe (Louvain, Belgium)
"Oxidations on Sulphur" and "Fluorine Substitutions in Radicals" (The W.K.R. Musgrave Lecture)

16.03.83 ✧ Dr. I. Gosney (Edinburgh)
"New Extrusion Reactions : Organic Synthesis in a Hot Tube"

25.03.83 ✧ Prof. F.G. Baglin (Nevada, USA)
"Interaction-Induced Raman Spectroscopy in Supercritical Ethane"

21.04.83 ✧ Prof. J. Passmore (New Brunswick, Canada)
"Novel Selenium-Iodine Cations"

04.05.83 ✧ Prof. P.H. Plesch (Keele)
"Binary Ionisation Equilibria Between Two Ions and Two Molecules. What Ostwald Never Thought Of"

10.05.83 ✧ Prof. K. Burger (Munich, West Germany)
"New Reaction Pathways from Trifluoromethyl-Substituted Heterodienes to Partially Fluorinated Heterocyclic Compounds"

11.05.83 ✧ Dr. N. Isaacs (Reading)
"The Application of High Pressures to the Theory and Practice of Organic Chemistry"

13.05.83 Dr. R. De Koch (Michigan/Amsterdam)
"Electronic Structural Calculations in Organometallic Cobalt Cluster Molecules. Implications for Metal Surfaces"

13.05.83 Dr. T.B. Marder (UCLA/Bristol)
"The Chemistry of Metal-Carbon and Metal-Metal Multiple Bonds"

16.05.83 Prof. R.J. Lagow (Texas, USA)
"The Chemistry of Polylithium Organic Compounds. An Unusual Class of Matter"

18.05.83 ✧ Dr. D.M. Adams (Leicester)
"Spectroscopy at Very High Pressures"

25.05.83 ✧ Dr. J.M. Vernon (York)
"New Heterocyclic Chemistry involving Lead Tetra-acetate"

15.06.83 Dr. A. Pietrzykowski (Warsaw/Strathclyde)
"Synthesis, Structure, and Properties of Aluminoxanes"

22.06.83 Dr. D.W.H. Rankin (Edinburgh)
"Floppy Molecules - the Influence of Phase on Structure"

05.07.83 ✧ Prof J. Miller (Camfinas, Brazil)
"Reactivity in Nucleophilic Substitution Reactions"

05.10.83 Prof. J.P. Maier (Basel, Switzerland)
"Recent Approaches to Spectroscopic Characterisation of Cations"

12.10.83 Dr. C.W. McLeland (Port Elizabeth, Australia)
"Cyclisation of Aryl Alcohols through the Intermediacy of Alkoxy Radicals and Aryl Radical Cations"

19.10.83 Dr. N.W. Alcock (Warwick)
"Aryl Tellurium (IV) Compounds, Patterns of Primary and Secondary Bonding"

26.10.83 Dr. R.H. Friend (Cavendish, Cambridge)
"Electronic Properties of Conjugated Polymers"

30.11.83 Prof. I.M.G. Gowie (Stirling)
"Molecular Interpretation of Non-Relaxation Processes in Polymer Glasses"

02.12.83 ✧ Dr. G.M. Brooke (Durham)
"The Fate of the Ortho-Fluorine in 3,3-Sigmatropic Reactions involving Polyflouro-Aryl and -Heteroaryl Systems"

14.12.83 Prof. R.J. Donovan (Edinburgh)
"Chemical and Physical Processes involving the Ion-Pair States of the Halogen Molecules"

10.01.84 ✧ Prof. R. Hester (York)
"Nanosecond Laser Spectroscopy of Reaction Intermediates"

18.01.84 ✧ Prof. R.K. Harris (UEA)
"Multi-Nuclear Solid-State Magnetic Resonance"

08.02.84 ✧ Dr. B.T. Heaton (Kent)
"Multi-Nuclear NMR Studies"

15.02.84 ✧ Dr. R.M. Paton (Edinburgh)
"Heterocyclic Syntheses using Nitrile Sulphides"

07.03.84 Dr. R.T. Walker (Birmingham)
"Synthesis and Biological Properties of some 5-Substituted Uracic Derivatives; Yet Another Example of Serendipity in Anti-Viral Chemotherapy"

21.03.84 Dr. P. Sherwood (Newcastle)
"X-Ray Photoelectron Studies of Electrode and Other Surfaces"

21.03.84 ✧ Dr. G. Beamson (Durham/Kratos)
"EXAFS ; General Principles and Applications"

23.03.84 Dr. A. Coulemans (Leuven)
"The Development of Field-Type Models of the Bonding in Molecular Clusters"

02.04.84 Prof. K. O'Driscoll (Waterloo)
"Chain Ending Reactions in Free Radical Polymerisation"

03.04.84 Prof. C.H. Rochester (Dundee)
"Infra-Red Studies of Adsorption at the Solid-Liquid Interface"

25.04.84 ✧ Dr. R.M. Acheson (Biochemistry, Oxford)
"Some Heterocyclic Detective Stories"

27.04.84 Dr. T. Albright (Houston, Texas)
"Sigmatropic Rearrangements in Organometallic Chemistry"

14.05.84 ✧ Prof. W.R. Dolbier (Florida, USA)
"Cycloaddition Reactions of Fluorinated Allenes"

16.05.84 Dr. P.J. Garratt (UCL)
"Syntheses with Dilithiated Vicinal Diesters and Carboximides"

22.05.84 Prof. F.C. De Schryver (Leuven)
"The Use of Luminescence in the Study of Micellar Aggregates" and "Configurational and Conformational Control in Excited State Complex Formation"

23.05.84 ✧ Prof. M. Tada (Waseda, Japan)
"Photochemistry of Dicyanopyrazine Derivatives"

31.05.84 Dr. A. Haaland (Oslo)
"Electron Diffraction Studies of some Organometallic Compounds"

11.06.84 ✧ Dr. J.B. Street (IBM, California)
"Conducting Polymers Derived From Pyrroles"

19.09.94 ✧ Dr. C. Brown (IBM, California)
"New Superbase Reactions with Organic Compounds"

21.09.84 Dr. H.W. Gibson (Signal UOP, Illinois)
"Isomerisation of Polyacetylene"

19.10.84 Dr. A. Germain (Languedoc, Montpellier)
"Anodic Oxidation of Perfluoro-Organic Compounds in Perfluoroalkane Sulphonic Acids"

24.10.84 Prof. R.K. Harris (Durham)
"NMR of Solid Polymers"

28.10.84 Dr. R. Snaith (Strathclyde)
"Exploring Lithium Chemistry : Novel Structures, Bonding, and Reagents"

07.11.84 ✧ Prof. W.W. Porterfield (Hampden-Sydney College, USA)
"There Is No Borane Chemistry (Only Geometry)"

07.11.84 Dr. H.S. Munro (Durham)
"New Information from ESCA Data"

21.11.84 Mr. N. Everall (Durham)
"Picosecond Pulsed Laser Raman Spectroscopy"

27.11.84 Dr. W.J. Feast (Durham)
"A Plain Man's Guide to Organic Metals"

28.11.84 Dr. T.A. Stephenson (Edinburgh)
"Some Recent Studies in Platinum Metal Chemistry"

12.12.84 Dr. K.B. Dillon (Durham)
"Phosphorus-31 NMR Studies of some Anionic Phosphorus Complexes"

11.01.85 ✧ Emeritus Prof. H. Suschitzky (Salford)
"Fruitful Fissions of Benzofuroxanes and Isobenzimidazoles (Umpolung of o-Phenylenediamine)

13.02.85 Dr. G.W.J. Fleet (Oxford)
"Synthesis of some Alkaloids from Carbohydrates"

19.02.85 ✧ Dr. D.J. Mincher (Durham)
"Stereoselective Synthesis of some Novel Anthracyclinones related to the Anti-Cancer Drug Adriamycin and to the Steffimycin Antibiotics"

27.03.85 Dr. R.E. Mulvey (Durham)
"Some Unusual Lithium Comlexes"

06.03.85 Dr. P.J. Kocienski (Leeds)
"Some Synthetic Applications of Silicon Mediated Annulation Reactions"

07.03.85 Dr. P.J. Rodgers (ICI plc Agricultural Division, Billingham)
"Industrial Polymers from Bacteria"

12.03.85 ✧ Prof. K.J. Packer (BP Ltd/East Anglia)
"NMR Investigations of the Structure of Solid Polymers"

14.03.85 ✧ Prof. A.R. Katritzky FRS (Florida)
"Some Adventures in Heterocyclic Chemistry"

20.03.85 Dr. M. Poliakoff (Nottingham)
"New Methods for Detecting Organometallic Intermediates in Solution"

28.03.85 Prof. H. Ringsdorf (Mainz)
"Polymeric Liposomes as Models for Biomembranes and Cells?"

24.04.85 ✧ Dr. M.C. Grossel (Bedford College, London)
"Hydroxypyridone Dyes - Bleachable One-Dimensional Metals?"

25.04.85 ✧ Major S.A. Shackleford (USAF)
"In-Situ Mechanistic Studies on Condensed Phase Thermochemical Reaction Processes : Deuterium Isotope Effects in HMX Decomposition, Explosives and Combustion"

01.05.85 ✧ Dr. D. Parker (ICI plc Petrochemicals and Plastics Division, Wilton)
"Applications of Raioisotopes in Industrial Research"

07.05.85 Prof. G.E. Coates (Formerly of University of Wyoming, USA)
"Chemical Education in England and America : Successes and Deficiencies"

08.05.85 Prof. D. Tuck (Windsor, Ontario)
"Lower Oxidation State Chemistry of Indium"

08.05.85 Prof. G. Williams (UCW, Aberystwyth)
"Liquid Crystalline Polymers"

09.05.85 Prof. R.K. Harris (Durham)
"Chemistry In A Spin : Nuclear Magnetic Resonance"

14.05.85 Prof. J. Passmore (New Brunswick, Canada)
"The Synthesis and Characterisation of some Novel Selenium-Iodine Cations, Aided by Selenium-77 NMR Spectroscopy"

15.05.85 ✧ Dr. J.E.Packer (Auckland, New Zealand)
"Studies of Free Radical Reactions in Aqueous Solution using Ionising Radiation"

17.05.85 Prof. I.D. Brown (McMaster University, Canada)
"Bond Valence as a Model for Inorganic Chemistry"

21.05.85 ✧ Dr. D.L.H. Williams (Durham)
"Chemistry in Colour"

22.05.85 Dr. M. Hudlicky (Blacksburg, USA)
"Preferential Elimination of Hydrogen Fluoride from Vicinal Bromofluoro-Compounds

22.05.85 ✧ Dr. R. Grimmett (Otago, New Zealand)
"Some Aspects of Nucleophilic Substitution in Imidazoles"

04.06.85 Dr. P.S. Belton (Food Research Institute, Norwich)
"Analytical Photoacoustic Spectroscopy"

13.06.85 Dr. D. Woolins (Imperial College, London)
"Metal-Sulphur-Nitrogen Complexes"

14.06.85 ✧ Prof. Z. Rappoport (Hebrew University, Jerusalem)
"The Rich Mechanistic World of Nucleophilic Vinylic Substitution"

19.06.85 Dr. T.N. Mitchell (Dortmund)
"Some Synthetic and NMR-Spectroscopic Studies of Organotin Compounds"

26.06.85 ✧ Prof. G. Shaw (Bradford)
"Synthetic Studies on Imidazole Nucleosides and the Antibiotic Coformycin"

12.07.85 ✧ Dr. K. Laali (Hydrocarbon Research Institute, University of Southern California)
"Recent Developments in Superacid Chemistry and Mechanistic Considerations in Electrophilic Aromatic Substitutions ; A Progress Report"

Lectures organised by Durham University Chemical Society during the period October 1982 - September 1985

14.10.85 ✧ Mr. F. Shenton (County Analyst, Durham)
"There is Death in the Pot"

28.10.82 Prof. M.F. Lappert FRS (Sussex)
"The Chemistry of some Unusual Subvalent Compounds of the Main Group IV and V Elements"

04.11.82 ✧ Dr. D.H. Williams (Cambridge)
"Studies on the Structures and Modes of Action of Antibiotics"

11.11.82 Dr. J. Cramp (ICI plc)
"Lasers in Industry"
(Joint Lecture with the Society of Chemical Industry)

25.11.82 Dr. D.H. Richards (PERME, MoD)
"Terminally Functional Polymers - their Synthesis and Uses"

27.01.83 Prof. D.W.A. Sharp (Glasgow)
"Some Redox Reactions in Fluorine Chemistry"

03.02.83 Dr. R. Manning (Zoology, Durham)
"Molecular Mechanisms of Hormone Action"

10.02.83 ✧ Sir G. Allen (Unilever Ltd)
" 'U.K.' Research"

17.02.83 Prof. A.G. MacDiarmid (Pennsylvania)
"Metallic Covalent Polymers $(SN)_x$ and $(CH)_x$ and their Derivatives"
(RSC Centenary Lecture)

03.04.83 ✧ Prof. A.C.T. North (Leeds)
"The Use of a Computer Display System in Studying Molecular Structures and Interactions"

20.10.83 ✧ Prof. R.B. Cundall (Salford)
"Explosives"

03.11.83 Dr. G. Richards (Oxford)
"Quantum Pharmacology"

10.11.83 ✧ Prof. J.H. Ridd (UCL)
"Ipso-Attack in Electrophilic Aromatic Substitution"

17.11.83 Dr. J. Harrison (Sterling Organic)
"Applied Chemistry and the Pharmaceutical Industry"
(Joint Lecture with the Society of Chemical Industry)

24.11.83 Prof. D.A. King (Liverpool)
"Chemistry in 2-Dimensions"

01.12.83 ✧ Dr. J.D. Coyle (The Open University)
"The Problem with Sunshine"

26.01.84 Prof. T.L. Blundell (Birkbeck College, London)
"Biological Recognition : Interactions of Macro-molecular Surfaces"

02.02.84 Prof. N.B.H. Jonathan (Southampton)
"Photoelectron Spectroscopy - a Radical Approach"

16.02.84 Prof. D. Phillips (The Royal Institution)
"Luminescence and Photochemistry - A Light Entertainment"

23.02.84 Prof. F.G.A. Stone FRS (Bristol)
"The Use of Carbene and Carbyne Groups to Synthesise Metal Clusters"
(The Waddington Memorial Lecture)

01.03.84 Prof. A.J. Leadbetter (Rutherford Appleton Labs.)
"Liquid Crystals"

08.03.84 Prof. D. Chapman (Royal Free Hospital School of Medicine, London)
"Phospholipids and Biomembranes, Basic Science and Future Techniques"

28.03.84 Prof. R. Schmidbaur (Munich)
"Ylides in the Coordination Sphere of a Metal : Synthetic, Structural, and Theoretical Aspects"
(RSC Centenary Lecture)

18.10.84 ✧ Dr. N. Logan (Nottingham)
"N_2O_4 and Rocket Fuels"

25.10.84 Dr. W.J. Feast (Durham)
"Synthesis of Conjugated Polymers. How and Why?"

08.11.84 Prof. B.J. Aylett (Queen Mary College, London)
"Silicon - Dead Common or Refined?"

15.11.84 ✧ Prof. B.T. Golding (Newcastle upon Tyne)
"The Vitamin B_{12} Mystery"

22.11.84 ✧ Prof. D.T. Clark (ICI New Science Group)
"Structure, Bonding, Reactivity, and Synthesis as Revealed by ESCA"
(RSC Tilden Lecture)

29.11.84 ✧ Prof. C.J.M. Sterling (University College of North Wales, Bangor)
"Molecules Taking the Strain"

06.12.84 Prof. R.D. Chambers (Durham)
"The Unusual World of Fluorine"

24.01.85 Dr. A.K. Covington (Newcastle upon Tyne)
"Chemistry with Chips"

31.01.85 Dr. M.L.H. Green (Oxford)
"Naked Atoms and Negligee Ligands"

07.02.85 ✧ Prof. A. Ledwith (Pilkington Bros.)
"Glass as a High Technology Material"
(Joint Lecture with the Society of Chemical Industry)

14.02.85 ✧ Dr. J.A. Salthouse (Manchester)
"Son et Lumiere"

21.02.85 ✧ Prof. P.M. Maitlis FRS (Sheffield)
"What Use is Rhodium?"

07.03.85 ✧ Dr. P.W. Atkins (Oxford)
"Magnetic Reactions"

First Year Induction Couse, October 1982

This course consisted of a series of one-hour lectures on the services available in the Department.

1. Departmental Organisation
2. Safety Matters
3. Electrical Appliances and Infra-Red Spectroscopy
4. Chromatography and Microanalysis
5. Atomic Absorption and Inorganic Analysis
6. Library Facilities
7. Mass Spectrometry
8. Nuclear Magnetic Resonance
9. Glassblowing Techniques

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